CHAPTER 10

Uveitis

Introduction

Classification

Uveitis, by strict definition, is an inflammation of the uveal tract. However, the term is now used to describe many forms of intraocular inflammation involving not only the uvea, but also adjacent structures. Uveitis may be classified on the basis of (a) *anatomy*, (b) *clinical features* and (c) *aetiology*.

Anatomical classification (Fig. 10.1)

1. **Anterior uveitis** may be subdivided into:
   a. ***Iritis***, in which inflammation predominantly affects the iris.
   b. ***Iridocyclitis***, in which both the iris and the anterior part of the ciliary body (pars plicata) are equally involved.
2. **Intermediate uveitis** is characterized by involvement predominantly of the posterior part of the ciliary body (pars plana), the extreme periphery of the retina and the underlying choroid.
3. **Posterior uveitis** involves inflammation of the choroid and retina posterior to the vitreous base.
4. **Panuveitis** implies involvement of the entire uveal tract.

> *NB:* Anterior uveitis is the most common type, followed by intermediate, posterior and panuveitis.

Clinical classification

According to the mode of onset and duration, uveitis may be acute or chronic.

1. **Acute uveitis** usually has a sudden, symptomatic onset and persists for up to 3 months. If the inflammation recurs following the initial attack, it is referred to as recurrent acute.
2. **Chronic uveitis** persists for longer than 3 months. The onset is frequently insidious and may be asymptomatic, although acute or subacute exacerbations may occur.

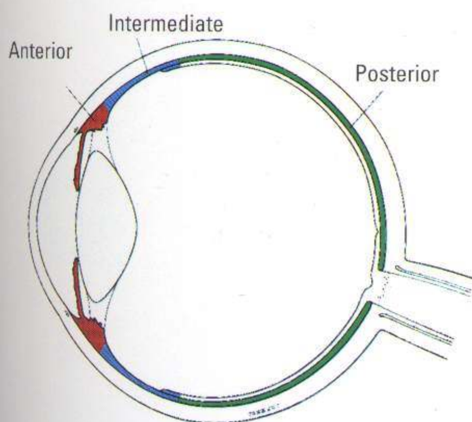


Fig. 10.1
Anatomical classification of uveitis

Aetiological classification

Exogenous uveitis is caused by external injury to the uvea or invasion by micro-organisms (or other agents) from without. Endogenous uveitis is caused by micro-organisms (or other agents) from within the patient. The following are the main types:

1. **Associated with a systemic disease** (e.g. sarcoidosis).
2. **Infections** with bacteria (e.g. tuberculosis), fungi (e.g. candidiasis) and viruses (e.g. herpes zoster).
3. **Infestations** with protozoa (e.g. toxoplasmosis) or nematodes (e.g. toxocariasis).
4. **Idiopathic specific uveitis entities** are a group of unrelated disorders unassociated with underlying systemic disease but with special characteristics of their own warranting independent description (e.g. Fuchs uveitis syndrome).
5. **Idiopathic non-specific uveitis entities** which do not fall into any of the above categories consititute about 25% of cases.

Clinical features

Anterior uveitis

Symptoms

1. **Acute anterior uveitis** is characterized by photophobia, pain, redness, decreased vision and lacrimation.
2. **Chronic anterior uveitis** may be asymptomatic or give rise to mild redness and the perception of floaters.

Signs

1. **Circumcorneal (ciliary) injection** in acute anterior uveitis has a violaceous hue (Fig. 10.2).
2. **Keratic precipitates** (KP) are cellular deposits on the coneal endothelium. Their characteristics and distribution may indicate the probable type of uveitis. KP most

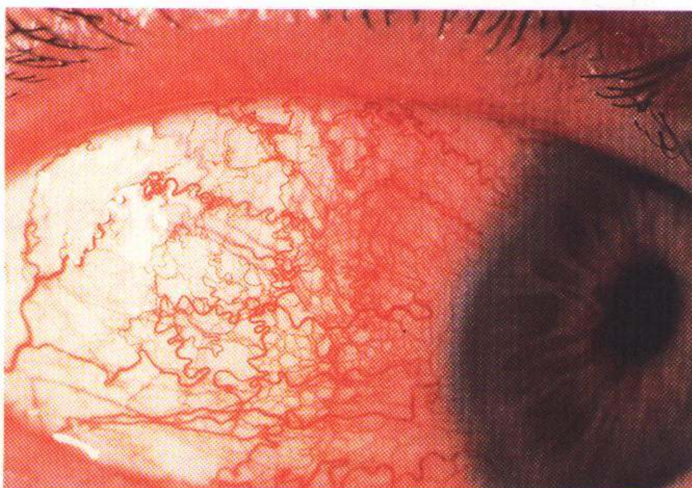


Fig. 10.2
Ciliary injection in acute anterior uveitis

commonly form in the mid and inferior zones of the cornea, due to convection currents in the anterior chamber. However, in Fuchs uveitis syndrome, they are scattered throughout the endothelium.

a. ***Endothelial dusting*** by myriads of cells occurs in acute anterior uveitis, as well as during subacute exacerbations of chronic inflammation (Fig. 10.3).

b. ***Medium-size*** KP occur in most types of acute and chronic anterior uveitis (Fig. 10.4).

c. ***Large*** KP are usually of the 'mutton fat' variety, with a greasy, waxy appearance, typically occurring in granulomatous uveitis (Fig. 10.5).

d. ***Old*** KP are pigmented (Fig. 10.6) and, if large, may develop a 'ground-glass' (hyalinized) appearance (Fig. 10.7).

3. Cells are indicative of active inflammation.

a. ***Aqueous cells*** are graded according to the number observed in an oblique slit beam, 3 mm long and 1 mm wide, with maximal light intensity and magnification.

- <5 cells = +/–
- 5–10 cells = +1
- 11–20 cells = +2
- 21–50 cells = +3
- >50 cells = +4
- hypopyon (Fig. 10.8)



Fig. 10.5
Mutton fat keratic precipitates

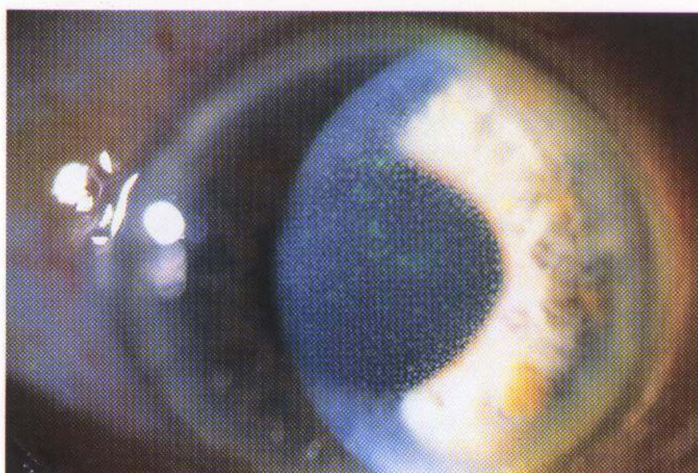


Fig. 10.3
Endothelial dusting in acute anterior uveitis



Fig. 10.6
Old pigmented keratic precipitates

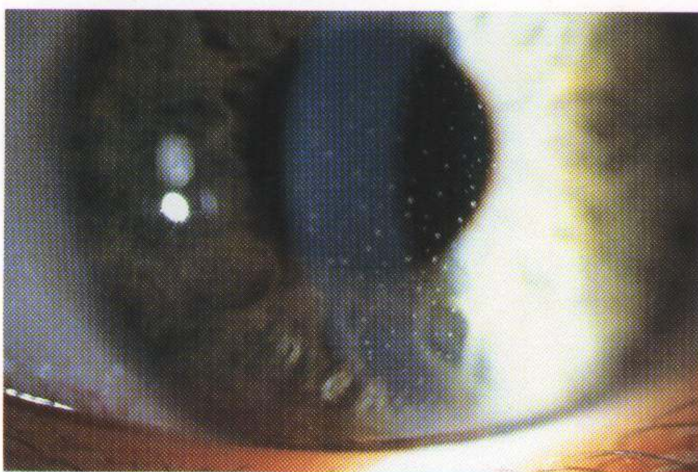


Fig. 10.4
Medium-size keratic precipitates

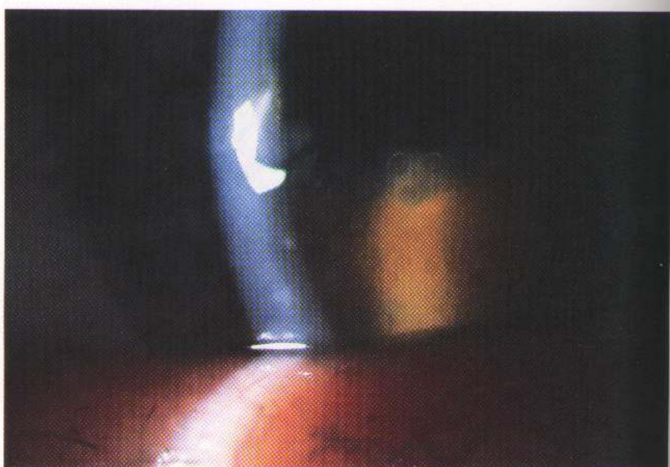
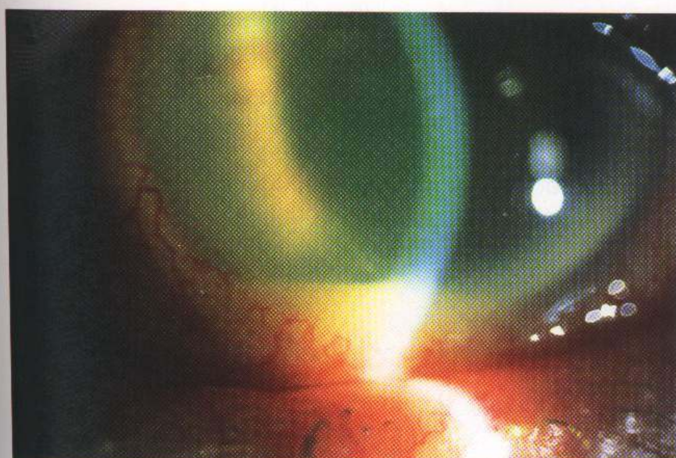


Fig. 10.7
Old 'ground-glass' keratic precipitates


Fig. 10.8
Hypopyon in acute anterior uveitis

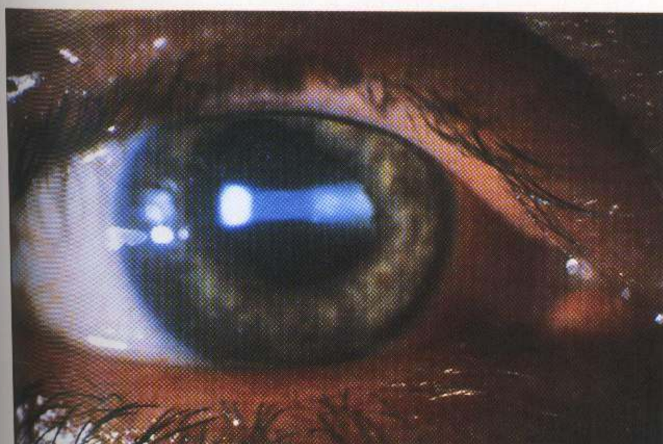
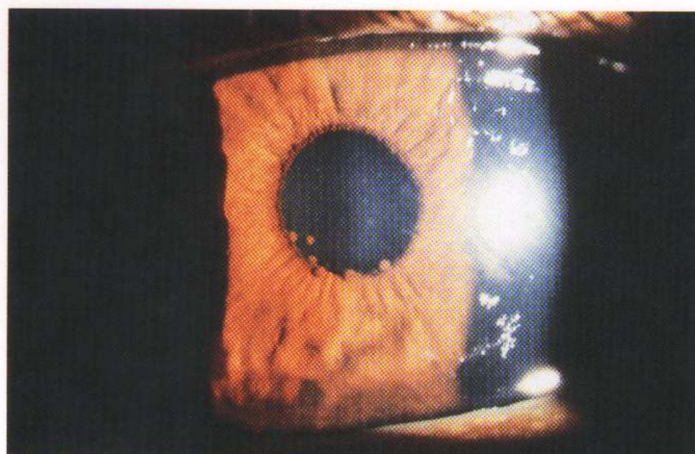
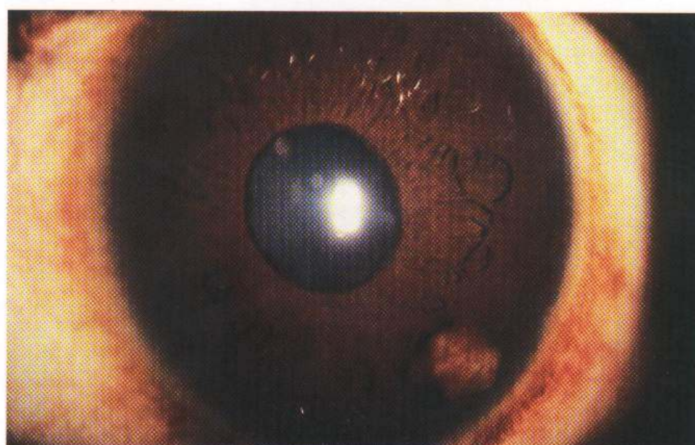

Fig. 10.9
Dense aqueous flare


Fig. 10.10
Fibrinous exudate in severe acute anterior uveitis

b. *Anterior vitreous cells* should be compared in number with those in the aqueous. In iritis, aqueous cells far exceed the number of vitreous cells.


Fig. 10.11
Koeppe nodules in granulomatous anterior uveitis


Fig. 10.12
Busacca nodule in granulomatous anterior uveitis

4. **Aqueous flare** is due to scattering of light (Tyndall effect) by proteins that have leaked into the aqueous humour through damaged iris blood vessels (Fig. 10.9). In the absence of cells, aqueous flare is not indicative of active inflammation and does not merit treatment. It is graded using the same setting on the slit-lamp as for cells.
   - faint: just detectable = +1
   - moderate: iris details clear = +2
   - marked: iris details hazy = +3
   - intense with fibrinous exudate = +4 (Fig. 10.10).
5. **Iris nodules** are a feature of granulomatous inflammation.
   a. *Koeppe* nodules are small and situated at the pupillary border (Fig. 10.11).
   b. *Busacca* nodules are less common and located away from the pupil (Fig. 10.12).

Complications

1. **Posterior synechiae** are adhesions between the iris and anterior lens capsule, which may form with ease during an attack of acute anterior uveitis and also in eyes with

moderate-to-severe chronic anterior uveitis (Fig. 10.13). Posterior synechiae extending for 360° around the pupillary border (seclusio pupillae) prevent the passage of aqueous humour from the posterior to the anterior chamber, giving rise to a forward bowing of the peripheral iris (iris bombé) (Fig. 10.14). This may lead to closure of the angle of the anterior chamber by the peripheral iris, with secondary elevation of intraocular pressure (*see* Chapter 9). After the posterior synechiae have been broken down, an imprint of iris pigment may remain on the anterior lens capsule (Fig. 10.15).

2. **Other complications** of chronic or recurrent anterior uveitis include band keratopathy, cataract, glaucoma, macular oedema, cyclitic membrane formation and phthisis bulbi.

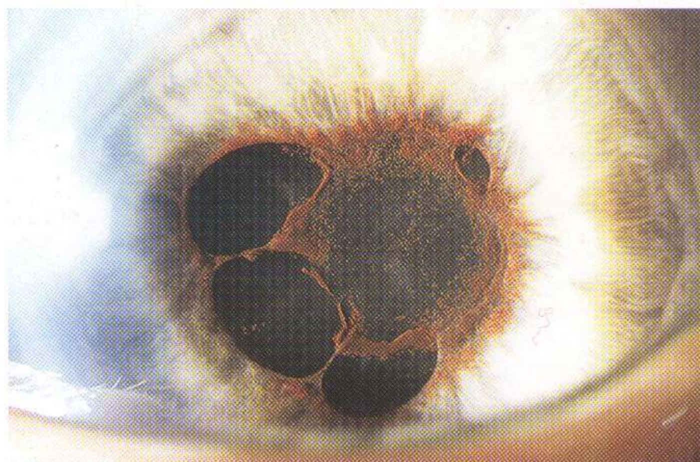


Fig. 10.13
Posterior synechiae

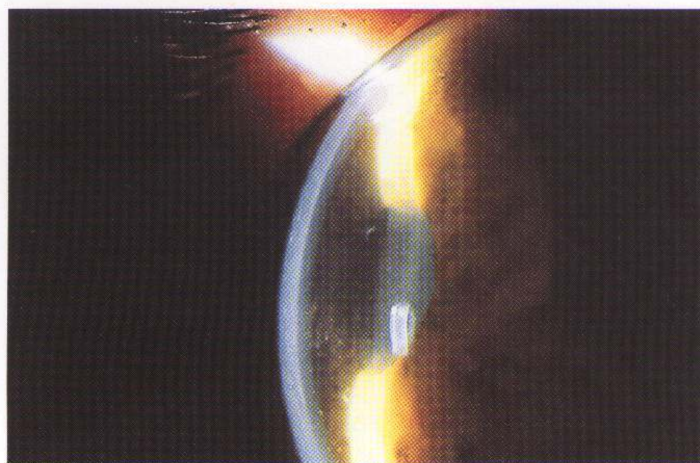


Fig. 10.14
Iris bombé

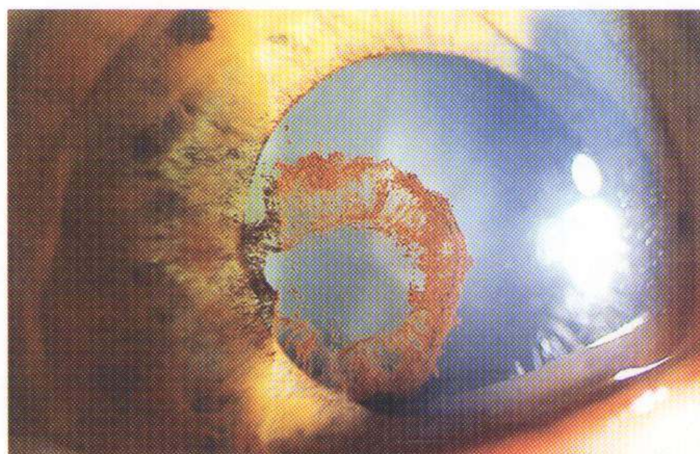


Fig. 10.15
Residual pigment following breakdown of posterior synechiae

Intermediate uveitis

1. **Symptoms** are initially floaters and later impairment of visual acuity due to cystoid macular oedema.
2. **Signs**. Cellular infiltration of the vitreous (vitritis) with fewer cells in the anterior chamber. Absence of focal inflammatory lesions in the posterior fundus.
3. **Complications** include cystoid macular oedema, cyclitic membrane formation, cataract and tractional retinal detachment.

   Intermediate uveitis is discussed in more detail later.

Posterior uveitis

Symptoms

These are floaters and impaired vision. A patient with a peripheral inflammatory lesion will complain of floaters and may have only minimal blurring of vision. On the other hand, active choroiditis involving the fovea or papillomacular bundle will primarily cause loss of central vision, and the patient may not notice vitreous opacities.

Signs

1. **Vitreous** signs include cells, flare, opacities (Fig. 10.16) and posterior vitreous detachment. The posterior hyaloid face may be covered by inflammatory precipitates comparable to KP.

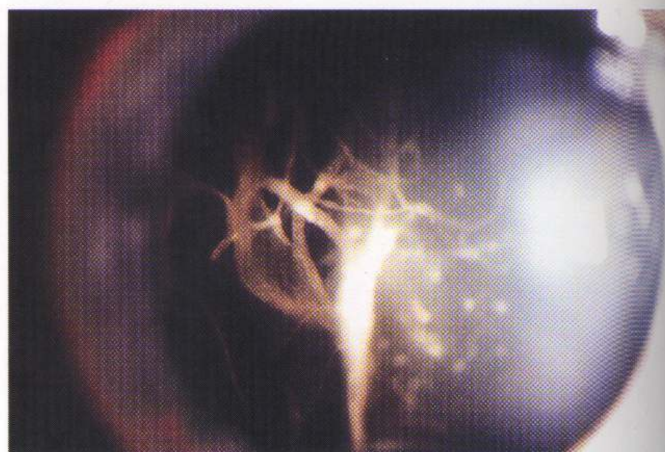


Fig. 10.16
Coarse vitreous opacities in posterior uveitis

2. **Choroiditis** is characterized by deep, yellow or greyish patches with fairly well-demarcated borders (Fig. 10.17). Inactive lesions appear as white, well-defined areas of chorioretinal atrophy with pigmented borders (Fig. 10.18).

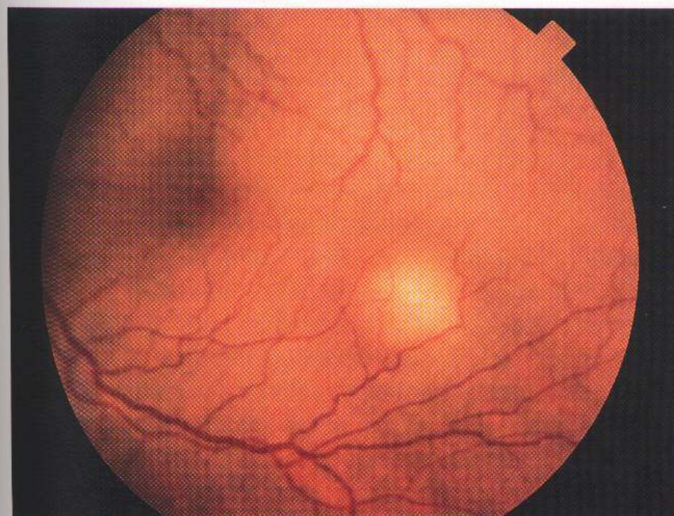


Fig. 10.17
Active focal choroiditis

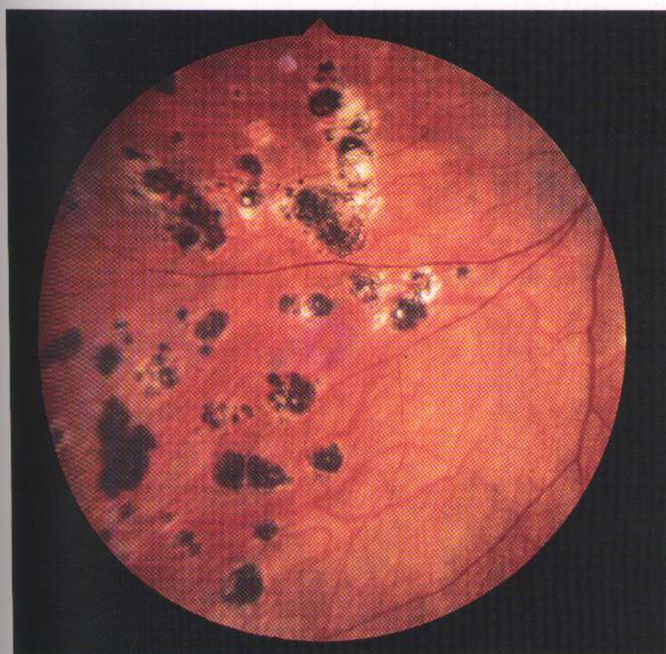


Fig. 10.18
Old multifocal choroiditis

3. **Retinitis** gives the retina a white cloudy appearance, with obscuration of retinal vessels (Fig. 10.19). The outline of the inflammatory focus is indistinct, rendering exact demarcation between healthy and affected retina difficult.
4. **Vasculitis** most frequently involves retinal veins (periphlebitis) and less commonly arteries (periarteritis). Active periphlebitis is characterized by a fluffy white haziness surrounding the blood column (Fig. 10.20). Involvement is patchy, with irregular extensions outside the vessel wall. Perivascular accumulation of granulomatous tissue in severe periphlebitis may give rise to 'candlewax drippings' (*see* Fig. 10.29).

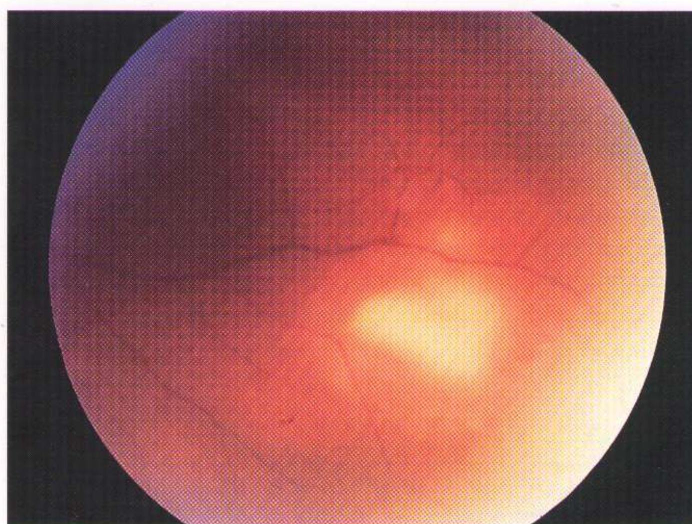


Fig. 10.19
Active focal retinitis

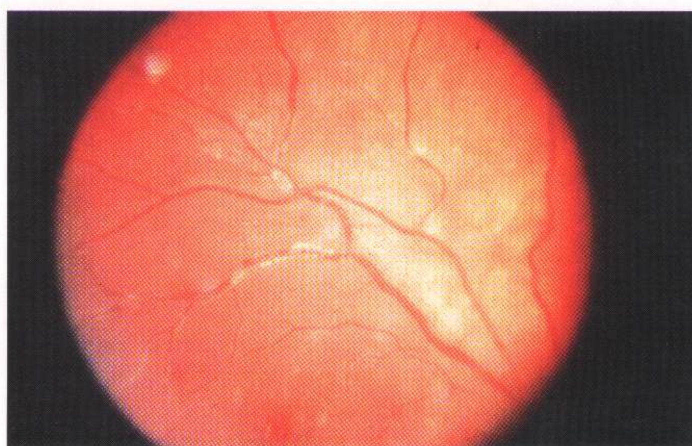


Fig. 10.20
Active periphlebitis

5. **'Spill-over' anterior uveitis** is common.

Complications

These include direct involvement of the macula by the inflammatory process, cystoid macular oedema, macular ischaemia, epiretinal membrane formation, vascular occlusions, choroidal neovascularization, retinal detachment and consecutive optic neuropathy.

Morphological classification

1. **Focal** in which there is a solitary inflammatory focus (e.g. toxoplasmosis).
2. **Multifocal** in which there are several separate foci (e.g. birdshot retinochoroidopathy).
3. **Geographical** in which there is a large confluent area of inflammation (e.g. cytomegalovirus retinitis).

Treatment

The main aims of treating uveitis are to prevent vision-threatening complications, to relieve discomfort and to treat the underlying disease, if possible. The three groups of drugs in current use are (a) *mydriatics*, (b) *steroids* and (c) *systemic immunosuppressive agents*. Uveitis of infective aetiology should be treated with the appropriate antimicrobial or antiviral agent.

Mydriatics

Preparations

1. **Short-acting**:
   - Tropicamide (0.5% and 1%) has a duration of 6 hours.
   - Cyclopentolate (0.5% and 1%) has a duration of 24 hours.
   - Phenylephrine (2.5% and 10%) has a duration of 3 hours but no cycloplegic effects.
2. **Long-acting**: atropine 1% is the most powerful cycloplegic and mydriatic with a duration of action lasting up to 2 weeks.

Indications

1. **To promote comfort** by relieving spasm of the ciliary muscle and pupillary sphincter, usually with atropine, although it is usually unnecessary to use this agent for more than 1–2 weeks. Once the inflammation shows signs of subsiding it can be substituted by a short-acting mydriatic, such as tropicamide or cyclopentolate.
2. **To prevent formation of posterior synechiae** by using a short-acting mydriatic which keeps the pupil mobile. In mild cases of chronic anterior uveitis the mydriatic can be instilled once at bedtime to prevent difficulties with accommodation during the day. Moreover the pupil should not be kept constantly dilated because posterior synechiae can still form in the dilated position. In young children, constant uniocular atropinization may induce amblyopia.
3. **To break down recently formed synechiae** with intensive topical mydriatics (atropine, phenylephrine) or subconjunctival injections of Mydricaine (adrenaline, atropine and procaine).

Steroids

Steroids are the mainstay of treatment. They can be administered (a) *topically* as drops or ointment, (b) by *periocular injection*, (c) by *intravitreal injection* or (d) *systemically*. Steroids, by whatever route, should be generally commenced at a high dose, which is subsequently tapered, once the inflammation comes under control.

Topical administration

Topical steroids are useful only for anterior uveitis because they do not reach therapeutic levels behind the lens. Strong steroids such as dexamethasone, betamethasone and prednisolone are preferable to weaker preparations such as fluorometholone. A solution penetrates the cornea better than a suspension or ointment. Ointment can, however, be instilled at bedtime. The frequency of instillation of drops depends on the severity of inflammation and can vary from one drop every 5 minutes to a drop every other day.

1. **Treatment of acute anterior uveitis** is relatively straightforward and depends on the severity of inflammation. Administration is initially very frequent (e.g. every 15 minutes) for a few hours and then gradually tapered to q.i.d. after several days. Once the inflammation is well controlled the frequency can be further reduced by one drop/week and often discontinued altogether by 5–6 weeks. Tissue plasminogen activator (12.5 µg in 0.1 ml) injected into the anterior chamber (intracamerally) with a 25-gauge needle may dissolve fibrinous exudate and prevent subsequent pupil block glaucoma.
2. **Treatment of chronic anterior uveitis** is more difficult because the inflammation may last for months and even years. Acute exacerbations with +4 aqueous cells are initially treated in the same way as acute anterior uveitis. If the inflammation is controlled with no more than +1 aqueous cells, the rate of instillation can be gradually further reduced by one drop/month and then sometimes discontinued.

> ***NB:*** Following cessation of treatment, the patient should be re-examined within a few days to ensure that the uveitis has not recurred.

3. **Complications**
   a. ***Glaucoma*** in susceptible individuals (*see* Chapter 9).
   b. ***Cataract*** can be induced by both systemic and, less frequently, topical steroid administration. The risk increases with dose and duration of therapy.
   c. ***Corneal*** complications, which are uncommon, include secondary infection with bacteria and fungi, recrudescences of herpes simplex keratitis, and corneal melting, which may be enhanced by inhibition of collagen synthesis.
   d. ***Systemic*** side effects may occasionally occur following prolonged administration, particularly in children.

Periocular injections

1. **Advantages over topical administration**
   - Therapeutic concentrations behind the lens may be achieved.
   - Water-soluble drugs, incapable of penetrating the cornea when given topically, can enter the eye trans-sclerally, when given by periocular injection.
   - A long-lasting effect can be achieved with depot preparations such as triamcinolone acetonide (Kenalog) or methylprednisolone acetate (Depomedrone).

2. Indications

- Severe acute anterior uveitis, especially in patients with ankylosing spondylitis with a marked fibrinous exudate in the anterior chamber or hypopyon (*see* Figure 10.8).
- As an adjunct to topical or systemic therapy in resistant chronic anterior uveitis.
- Intermediate uveitis.
- Poor patient compliance with topical or systemic medication.
- At the time of surgery in eyes with uveitis.

3. Conjunctival anaesthesia

a. A topical anaesthetic such as amethocaine is instilled at 1-minute intervals for 5 minutes.

b. A small cotton pledget impregnated with amethocaine (or equivalent) is placed into the conjunctival sac at the site of injection and left there for 5 minutes.

4. Anterior sub-Tenon injection

a. 1 ml of steroid is drawn up into a 2 ml syringe and the drawing-up needle replaced with a 25-gauge 3/8-inch (10 mm) needle.

b. The patient is asked to look away from the site of injection: most frequently up.

c. With non-toothed forceps, the conjunctiva and Tenon capsule are grasped and lifted.

d. With the bevel away from the globe, the needle is passed through the conjunctiva and Tenon capsule at the point where they are grasped.

e. 0.5 ml of steroid is injected slowly.

5. Posterior sub-Tenon injection

a. 1.5 ml steroid is drawn up into a 2 ml syringe and the drawing-up needle replaced with a 25-gauge 5/8-inch (16 mm) needle.



Fig. 10.21
Posterior sub-Tenon steroid injection (Courtesy of V. Tanner)

b. The patient is asked to look away from the site of injection: most frequently inferonasally when the injection is being given superotemporally.

c. The bulbar conjunctiva is penetrated with the tip of the needle, bevel towards the globe, slightly on the global side of the fornix (Fig. 10.21).

d. The needle is slowly inserted posteriorly, following the contour of the globe, keeping it as close to the globe as possible. In order not to penetrate the globe accidentally, wide side-to-side motions are made as the needle is being inserted and the limbus watched; movement of the limbus means that the sclera has been engaged!

e. When the needle has been advanced to the hub and cannot be inserted any further, the plunger is slightly withdrawn and, if no blood has entered the syringe, 1 ml injected. If the needle is too far away from the globe, adequate trans-scleral absorption of steroid will not occur.

> ***NB:*** An alternative method is to incise the conjunctiva and Tenon's capsule, and to perform the injection with a blunt sub-Tenon or lacrimal cannula.

Intravitreal injection

Intravitreal steroid injection of triamcinolone acetonide (2 mg in 0.05 ml) is currently under evaluation. It has been used successfully in resistant uveitic chronic cystoid macular oedema.

Systemic therapy

1. Preparations

a. ***Oral*** prednisolone 5 mg is the main preparation. Enteric coated tablets are useful in patients with acid-peptic disease.

b. ***Injections*** of adrenocorticotrophic hormone (ACTH) are useful in patients intolerant to oral steroids.

2. Indications

- Intractable anterior uveitis resistant to topical therapy and anterior sub-Tenon injections.
- Intermediate uveitis unresponsive to posterior sub-Tenon injections.
- Certain types of posterior or panuveitis, particularly with severe bilateral involvement.

3. General rules of administration

- Start with a large dose and then reduce.
- A reasonable starting dose of prednisolone is 1 mg/kg per day given in a single morning dose.
- Once the inflammation is brought under control, reduce the dose gradually over several weeks.
- If steroids are given for less than 2 weeks there is no need for gradual reduction.

4. Side effects depend on the duration of administration.

a. ***Short-term*** therapy may cause dyspepsia, mental changes, electrolyte imbalance, aseptic necrosis of the head of the femur and, very rarely, hyperosmolar hyperglycaemic non-ketotic coma.

b. Long-term therapy may cause a Cushingoid state (*see* Chapter 20), osteoporosis, limitation of growth in children, reactivation of infections such as TB, cataract and increase in severity of pre-existing conditions such as diabetes and myopathy.

Immunosuppressive agents

Immunosuppressive agents used in the treatment of uveitis are (a) *antimetabolites* (cytotoxics) and (b) *T-cell inhibitors*.

Indications

1. **Sight-threatening uveitis**, which is usually bilateral, non-infectious, reversible and has failed to respond to *adequate* steroid therapy.
2. **Steroid-sparing therapy** in patients with intolerable side effects from systemic steroids. Once a patient has been started on an immunosuppressive drug and the appropriate dose ascertained, treatment should continue for 6–24 months, after which gradual tapering and discontinuation of medication should be attempted over the next 3–12 months. However some patients may require long-term therapy for control of disease activity.

Antimetabolites

1. **Azathioprine**
   a. Indications: mainly Behçet disease.
   b. Dose is 1–3 mg/kg per day (50 mg tablet) administered orally once daily or in divided doses.
   c. Side effects include bone marrow suppression, gastrointestinal disturbance and hepatotoxicity.
   d. Monitoring involves a complete blood count every 4–6 weeks and liver function tests every 12 weeks.
2. **Methotrexate**
   a. Indications include a variety of chronic non-infectious uveitides unresponsive to conventional steroid therapy.
   b. Dose is 7.5–25 mg in a single dose once weekly.
   c. Side effects: bone marrow suppression, hepatotoxicity and pneumonitis are serious but rarely occur with low-dose administration. The most common side effects are gastrointestinal.
   d. Monitoring involves full blood counts and liver function tests every 1–2 months.
3. **Mycophenolate mofetil**
   a. Indications are as yet not established but it may prove a useful alternative to other antimetabolites.
   b. Dose is 1 g b.d.
   c. Side effects include gastrointestinal disturbance and bone marrow suppression.
   d. Monitoring involves a full blood count initially weekly for 4 weeks and then less frequently.

T-cell inhibitors

1. **Cyclosporin**
   a. Indications include Behçet disease, intermediate uveitis, Vogt–Koyanagi–Harada syndrome, birdshot retinochoroidopathy, sympathetic ophthalmitis and retinal vasculitis.
   b. Dose is usually 2–5 mg/kg per day in two divided doses.
   c. Side effects include hypertension, nephrotoxicity, hirsutism, hepatotoxicity and gingival hyperplasia.
   d. Monitoring involves blood pressure, full blood count, renal and liver function tests every 6 weeks.
2. **Tacrolimus (FK 506)**
   a. Indications are not yet established. Currently the drug is being used as an alternative to cyclosporin in resistant cases or in patients who develop unacceptable adverse effects.
   b. Dose is 0.05—0.15 mg/kg per day.
   c. Side effects include nephrotoxicity, gastrointestinal disturbance, hyperglycaemia and neurological problems.
   d. Monitoring involves blood pressure, renal function tests and blood glucose, initially weekly and subsequently less frequently.

Uveitis in spondylarthropathies

Ankylosing spondylitis

Ankylosing spondylitis (AS) primarily involves the sacroiliac joints and axial skeleton. About 90% of patients are positive for HLA-B27 and some have associated inflammatory bowel disease (enteropathic arthritis) (*see* Chapter 20).

Acute anterior uveitis occurs in 30% of patients with AS; conversely, 30% of males with acute iritis will have AS. Although both eyes are rarely involved simultaneously, either eye is frequently affected at different times. In severe uveitis there may be a fibrinous anterior chamber exudate. There is no correlation between the severity and activity of eye and joint involvement. Despite the high rate of recurrence, the long-term visual prognosis is good and vision-threatening complications rare. In a few patients with many recurrent attacks the inflammation may eventually become chronic.

Reiter syndrome

Reiter syndrome is defined as an episode of peripheral arthritis of more than 1 month's duration occurring in association with urethritis or cervicitis, or both. About 70% of patients are positive for HLA-B27 and 60% have associated sacroiliitis (*see* Chapter 20).

1. **Acute anterior uveitis** occurs in about 20% of patients.
2. **Bilateral mucopurulent conjunctivitis** is the most common manifestation. It usually follows the urethritis by



Fig. 10.22
Keratitis in Reiter syndrome

about 2 weeks and precedes the arthritis. It usually resolves spontaneously within 7–10 days and does not require treatment. Cultures for bacteria are usually negative.

3. **Punctate epithelial keratitis** with subepithelial infiltrates may occur in isolation or in association with conjunctivitis (Fig. 10.22).

Psoriatic arthritis

Psoriatic arthritis affects about 7% of patients with psoriasis and is associated with an increased prevalence of HLA-B27 and HLA-B17 (*see* Chapter 20).

1. **Anterior uveitis**, which may be acute or chronic, is uncommon.
2. **Conjunctivitis** occurs in some patients.
3. **Keratitis** in the form of raised marginal corneal infiltrates develops in some patients with acute iritis.
4. **Secondary Sjögren syndrome** is uncommon.

Uveitis in juvenile arthritis

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is an uncommon, inflammatory arthritis of at least 6 weeks duration developing in children before the age of 16 years. Patients are seronegative for IgM rheumatoid factor. Based on the onset and the extent of joint involvement during the first 6 months, three modes of presentation are recognized: (a) *pauciarticular*, (b) *polyarticular* and (c) *systemic* (*see* Chapter 20). The main ocular manifestation is chronic anterior uveitis. Uveitis does not occur in patients with systemic onset JIA and is uncommon in polyarticular disease. At highest risk are children with early-onset pauciarticular involvement who are also positive for antinuclear antibodies (ANA) and carriers of HLA-DR5 in whom the incidence of uveitis is approximately 20%.

> *NB:* JIA is not synonymous with juvenile rheumatoid arthritis. The latter is the juvenile equivalent of adult rheumatoid arthritis and is not associated with uveitis.

Clinical features

The uveitis is chronic, non-granulomatous and bilateral in 70% of cases. It is unusual for unilateral uveitis to become bilateral after more than a year. When bilateral, the severity of inflammation is usually symmetrical.

1. **Presentation** is invariably asymptomatic; the uveitis is frequently detected on routine slit-lamp examination. Even during acute exacerbations with +4 aqueous cells, it is rare for patients to complain, although a few report an increase in floaters.
2. **Signs**
   - Uninjected eye even in the presence of severe uveitis.
   - Small to medium-size KP.
   - During acute exacerbations, the entire endothelium shows 'dusting', but hypopyon does not develop.
   - Posterior synechiae are common in long-standing undetected uveitis.
3. **Prognosis**
   - In about 10% of cases the uveitis is mild, with never more than +1 aqueous cells, and persists for less than 12 months.
   - About 15% of patients have one attack, which lasts less than 4 months, the severity of inflammation varying from +2 to +4 aqueous cells.
   - In 50% of cases, the uveitis is moderate to severe and persists for more than 4 months.
   - In 25% of cases, the uveitis is very severe, lasts for several years and responds poorly to treatment. In this subgroup, band keratopathy (Fig. 10.23) occurs in 40% of patients, cataract in 30% (Fig. 10.24) and secondary inflammatory glaucoma in 15%.

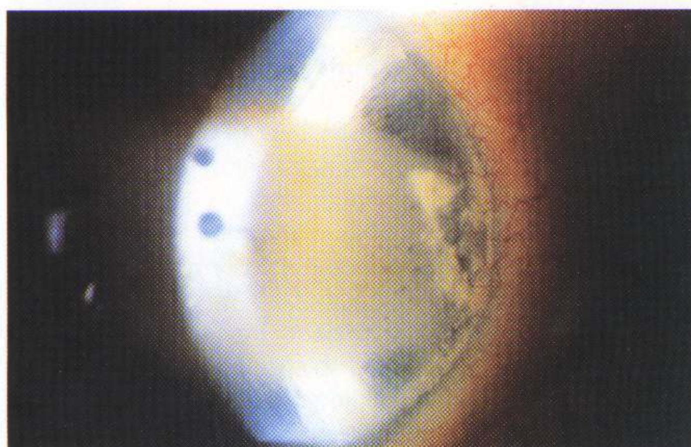


Fig. 10.23
Band keratopathy due to chronic anterior uveitis in juvenile idiopathic arthritis

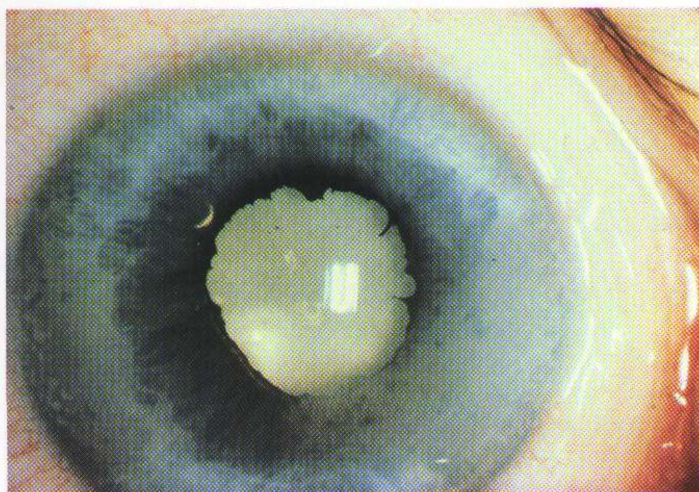


Fig. 10.24
Band keratopathy and cataract due to chronic anterior uveitis in juvenile idiopathic arthritis

Treatment

Topical steroids are usually effective; acute exacerbations require very frequent instillation. Poor responders to topical administration may benefit from periocular injections. Low-dose methotrexate is useful for steroid resistance.

Screening

Because the onset of intraocular inflammation is invariably asymptomatic, it is extremely important to regularly screen children at risk for at least 7 years from the onset of arthritis. The frequency of slit-lamp examination is governed by the various risk factors:

- Systemic onset = not required.
- Polyarticular onset = every 9 months.
- Polyarticular onset + ANA = every 6 months.
- Pauciarticular onset = every 4 months.
- Pauciarticular onset + ANA = every 3 months.

Other types of juvenile arthritis and uveitis

1. **Juvenile ankylosing spondylitis** is uncommon and typically affects boys around the age of 10 years. In contrast to adult AS, children tend to present with peripheral joint involvement but, like adults, some develop recurrent acute anterior uveitis.
2. **Juvenile Reiter syndrome** is rare and invariably post-dysenteric. A few cases of acute anterior uveitis have been reported.
3. **Juvenile psoriatic arthritis** is uncommon and may occasionally be associated with chronic anterior uveitis.
4. **Sarcoidosis** is rare in children and may present with arthropathy and anterior uveitis.
5. **Chronic infantile neurological cutaneous and articular/neonatal-onset multi-system inflammatory disease syndrome** (CINCA/NOMID) is a rare, idiopathic disease characterized by skin rash, arthropathy and involvement of the central nervous system. About 50% of children develop recurrent anterior uveitis.
6. **Lyme disease** (*see* Chapter 20).

Uveitis in inflammatory bowel disease

Ulcerative colitis

Ulcerative colitis is an idiopathic, chronic, relapsing disease involving the rectum and colon (*see* Chapter 20).

1. **Acute anterior uveitis** occurs in about 5% of patients and may synchronize with exacerbation of colitis. As expected, uveitis is commoner in patients with associated ankylosing spondylitis.
2. **Other manifestations**, which are uncommon, include peripheral corneal infiltrates, conjunctivitis and papillitis.

Crohn disease

Crohn disease is an idiopathic, chronic, relapsing disease most frequently involving the ileocaecal region (*see* Chapter 20).

1. **Acute anterior uveitis** occurs in about 3% of patients.
2. **Other manifestations,** occasionally encountered include conjunctivitis, episcleritis, peripheral corneal infiltrates and retinal periphlebitis.

Whipple disease

Whipple disease is a rare, bacterial, multi-system disease characterized by intestinal malabsorption and steatorrhoea.

1. **Uveitis** in the form of chronic iridocyclitis, vitritis and retinitis is rare.
2. **Other manifestations** include retrobulbar neuritis and other neuro-ophthalmic features.

Uveitis in nephritis

Tubulointerstitial nephritis

Tubulointerstitial nephritis and uveitis (TINU) is an uncommon hypersensitivity reaction, usually to a drug such as an antibiotic or a NSAID. It most frequently affects women and children. Renal disease usually precedes the uveitis.

1. **Presentation** is with constitutional symptoms, proteinuria, anaemia, hypertension and non-oliguric renal failure. The response to systemic steroid therapy is good and the condition resolves within a few months.
2. **Anterior uveitis**, usually bilateral, often become chronic and steroid-resistant. Immunosuppressive agents, however, are usually effective.

IgA glomerulonephritis

IgA glomerulonephritis is a common renal disease in which IgA is found in the glomerular mesangium.

1. **Presentation** is usually in the third to fifth decades with recurrent macroscopic haematuria which may be associated with upper respiratory tract infection.
2. **Ocular manifestations**, which are uncommon, include anterior uveitis, keratoconjunctivitis and scleritis.

Uveitis in non-infectious multi-system diseases

Sarcoidosis

Sarcoidosis is an idiopathic, granulomatous disease with frequent ocular manifestations (*see* Chapter 20). Uveitis occurs independently of the activity or severity of systemic disease, most commonly preceding or within 1 year of the onset of sarcoidosis.

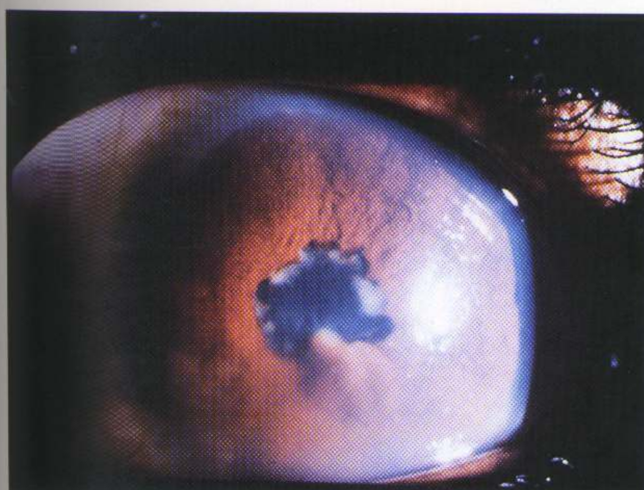


Fig. 10.25
Iris nodules in sarcoid granulomatous anterior uveitis



Fig. 10.26
Snowball opacities in sarcoid intermediate uveitis

Anterior uveitis

1. **Acute** anterior uveitis typically affects patients with acute-onset sarcoid. It can usually be controlled with topical treatment.
2. **Chronic granulomatous** anterior uveitis typically affects older patients with chronic pulmonary sarcoid and is characterized by mutton fat keratic precipitates and iris nodules (Fig. 10.25). Severe and long-standing inflammation may lead to secondary cataract, glaucoma, band keratopathy and cystoid macular oedema. Periocular or systemic steroids are often required.

Intermediate uveitis

Relatively uncommon, this is characterized by vitreous cells and snowball opacities (Fig. 10.26). Treatment is initially with posterior sub-Tenon steroids. Since sarcoidosis does not invariably produce systemic manifestations, it is important to rule out this possibility in patients with presumed idiopathic intermediate uveitis.

Posterior uveitis

The posterior segment is involved in about 25% of patients with ocular sarcoid.

1. **Retinal periphlebitis** may vary in severity from mild (Fig. 10.27) to severe (Fig. 10.28). Occasionally severe periphlebitis may be associated with perivenous exudates referred to as 'candlewax drippings' (Fig. 10.29) and

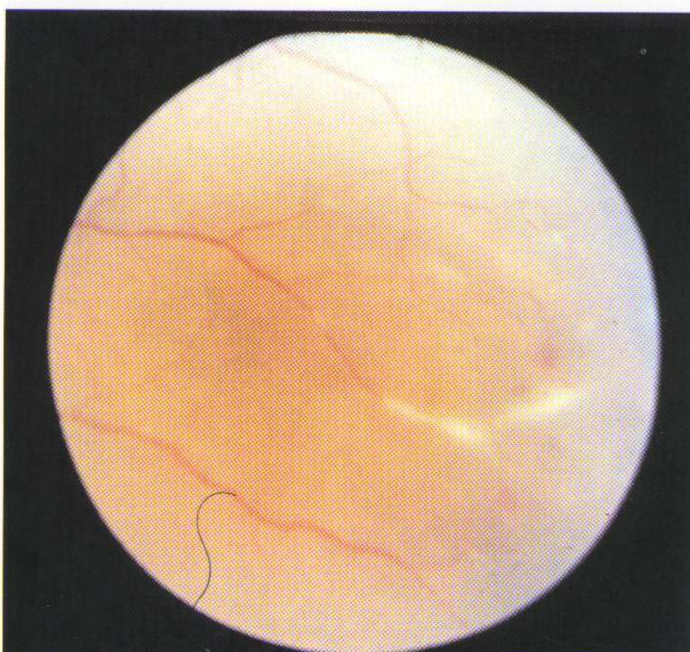
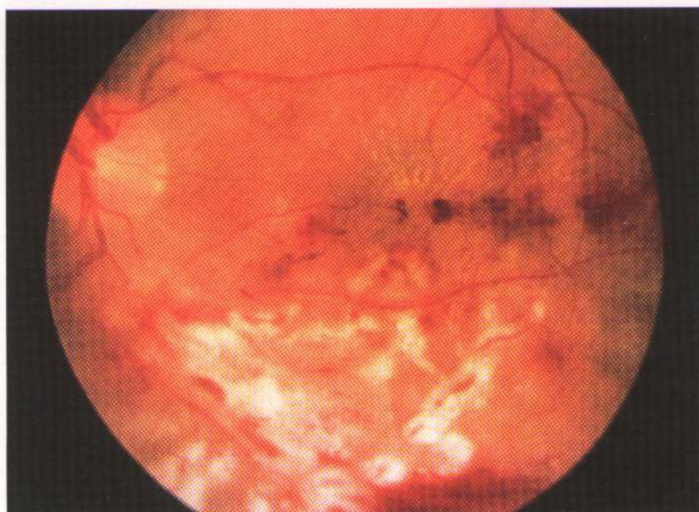
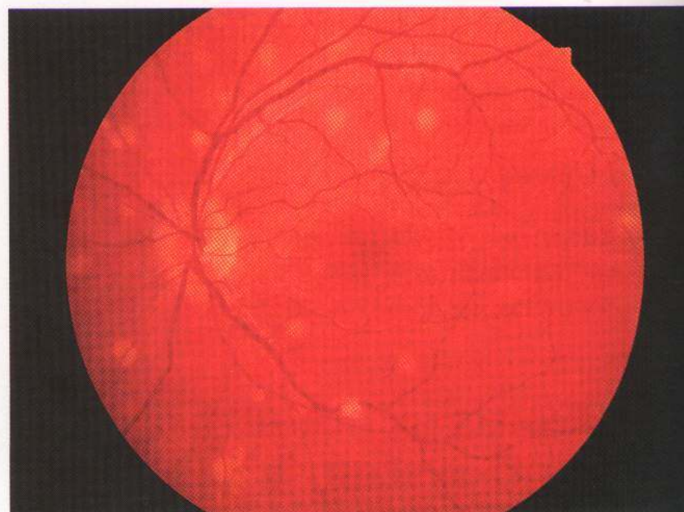
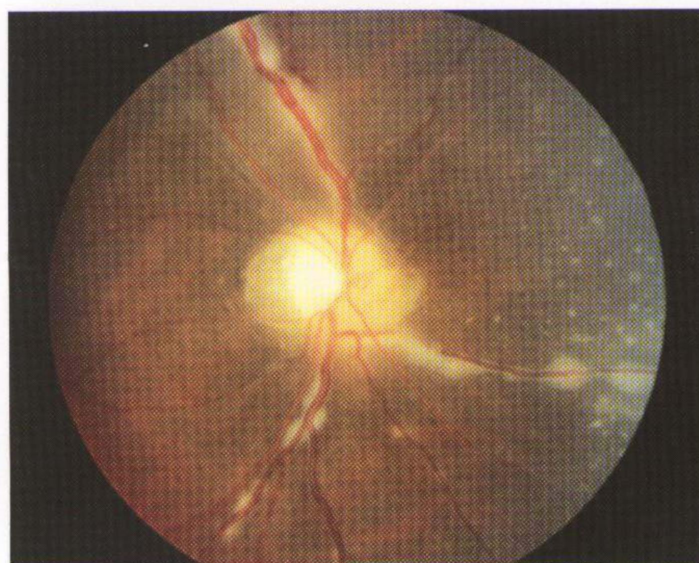
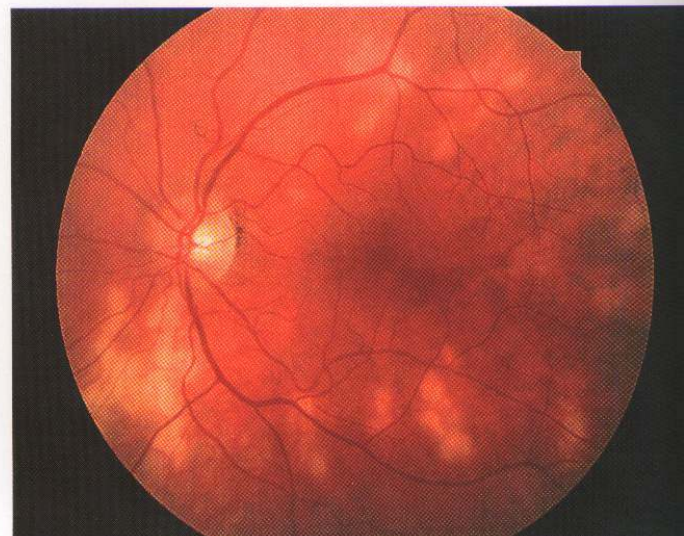


Fig. 10.27
Mild sarcoid periphlebitis (Courtesy of P. Morse)


Fig. 10.28
Severe sarcoid periphlebitis


Fig. 10.30
Small choroidal sarcoid granulomas


Fig. 10.29
'Candlewax drippings' in sarcoid periphlebitis (Courtesy of P. Morse)


Fig. 10.31
Confluent choroidal sarcoid infiltrates

branch retinal vein occlusion. Although acute lesions may resolve spontaneously or with systemic steroids, vascular sheathing, once established, is permanent.

2. **Choroidal** granulomas are relatively uncommon and vary in appearance:
   - Multiple, small, pale-yellow, infiltrates (Fig. 10.30).
   - Larger, confluent infiltrates with amoeboid margins are less common (Figs 10.31 and 10.32).
   - Large solitary choroidal granuloma (Fig. 10.33) is the least common and may be mistaken for an amelanotic choroidal melanoma.
3. **Retinal** granulomas are relatively uncommon and appear as white or yellow lesions (Fig. 10.34).
4. **Preretinal** granulomas, also uncommon, are typically located inferiorly, anterior to the equator (Landers sign) (Fig. 10.35).
5. **Optic disc granulomas** are rare and do not usually affect vision (Fig. 10.36).
6. **Peripheral retinal neovascularization** is an occasional finding (Fig. 10.37) which, in black patients, may be mistaken for that associated with sickle-cell retinopathy (*see* Chapter 14).

> ***NB:*** Papilloedema, usually secondary to involvement of the central nervous system, may occur in the absence of other eye lesions.

Treatment of posterior uveitis

Steroids are the mainstay of treatment. Prolonged steroid therapy is, however, often poorly tolerated, necessitating steroid-sparing options such as low-dose methotrexate which is a relatively safe and effective adjunct in chronic disease.

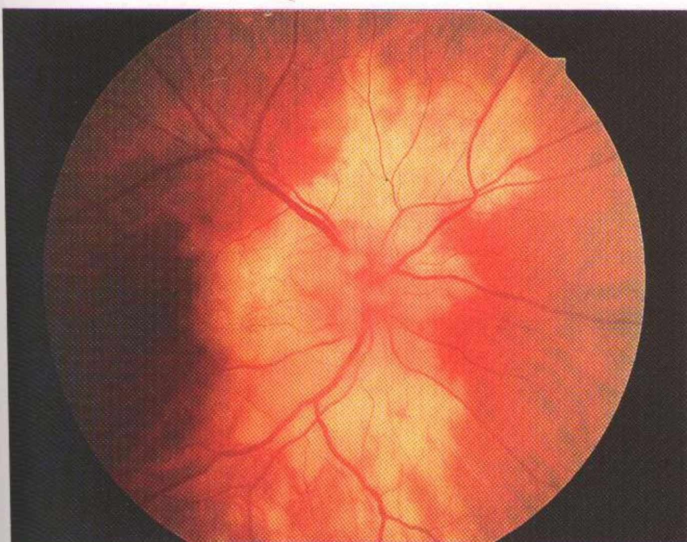


Fig. 10.32
Confluent parapapillary choroidal sarcoid granulomatous infiltration

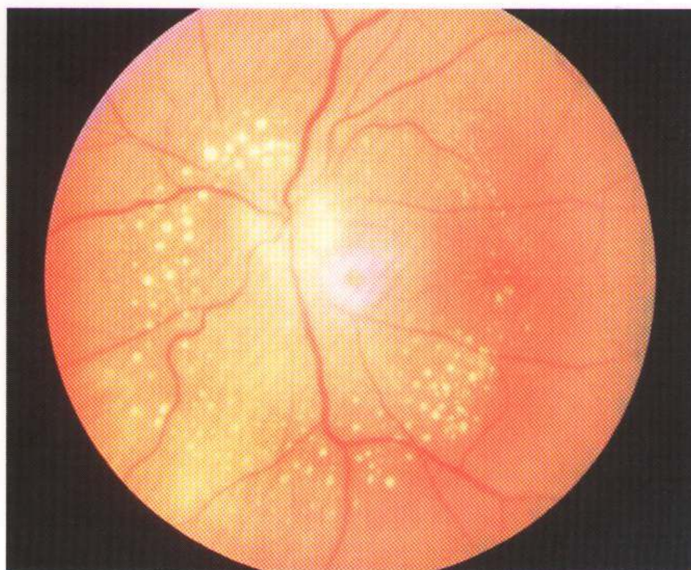


Fig. 10.34
Multiple retinal sarcoid granulomas

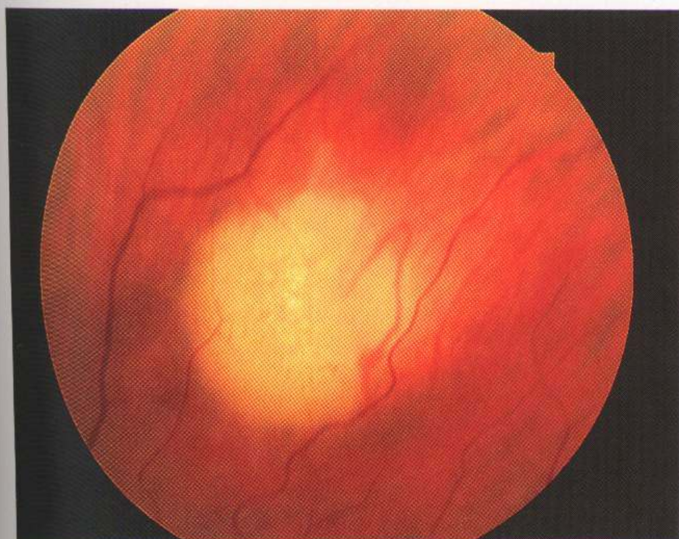


Fig. 10.33
Large solitary choroidal sarcoid granuloma

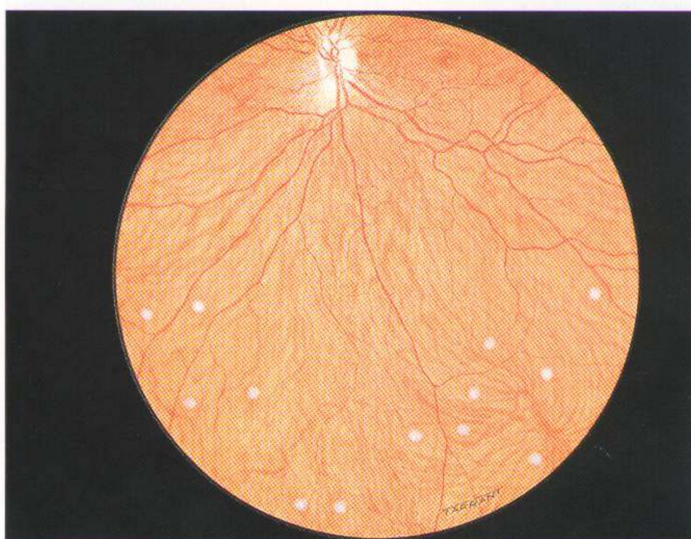
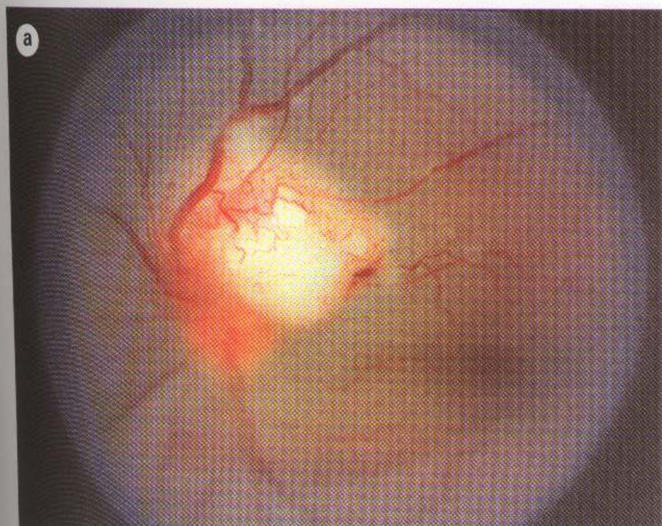


Fig. 10.35
Multiple preretinal sarcoid granulomas (Landers sign)



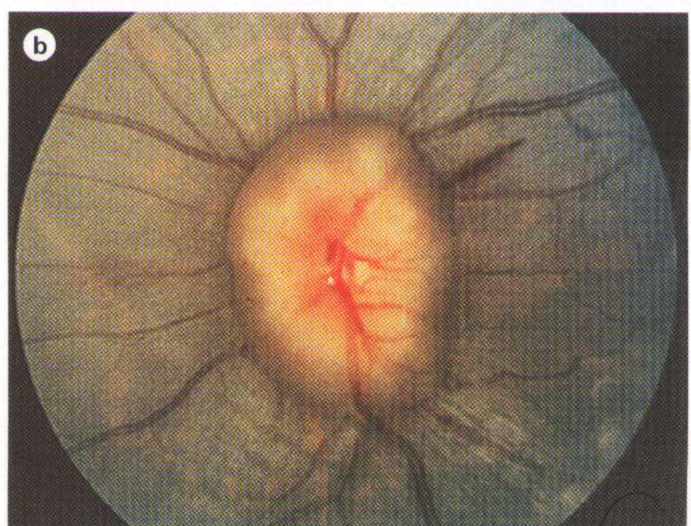


Fig. 10.36
Optic disc sarcoid granulomas (Courtesy of Wilmer Institute)

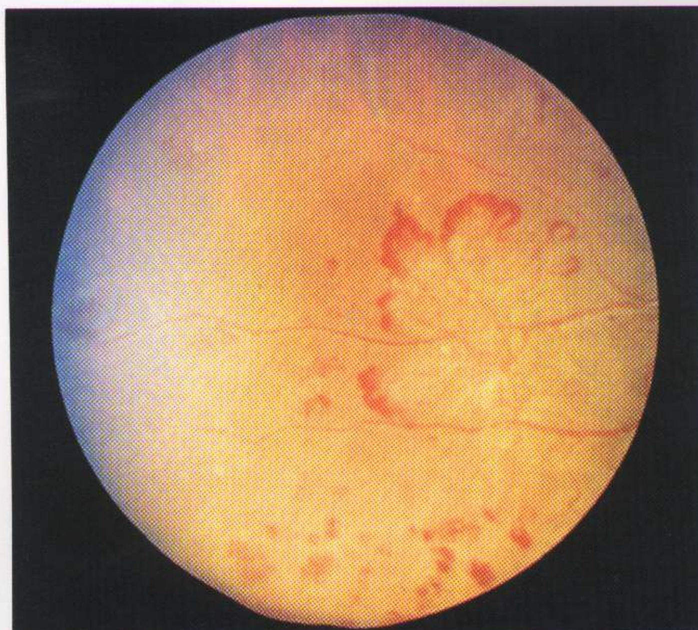


Fig. 10.37
Peripheral retinal neovascularization in sarcoidosis (Courtesy of P. Morse)

Differential diagnosis

1. **Intermediate uveitis** may be idiopathic or associated with Lyme disease, multiple sclerosis, non-Hodgkin large B-cell lymphoma and Whipple disease.
2. **Small choroidal lesions** also occur in multifocal choroiditis with panuveitis, birdshot chorioretinopathy and tuberculosis.
3. **Periphlebitis** also occurs in Behçet disease, tuberculosis, multiple sclerosis, cytomegalovirus retinitis, cat-scratch fever and Crohn disease.

Behçet disease

Behçet disease is an idiopathic disease which typically affects young men from the eastern Mediterranean region and Japan (*see* Chapter 20). Ocular manifestations, frequently bilateral, are seen in up to 95% of men and 70% of women. They usually follow, occasionally precede and rarely coincide with the onset of systemic symptoms.

Clinical features

1. **Presentation** is in the third to fourth decades with anterior or posterior uveitis.
2. **Acute recurrent anterior uveitis** may be simultaneously bilateral and is frequently associated with a transient mobile hypopyon (Fig. 10.38). Initially it responds well to topical steroids but subsequent chronicity may eventually lead to phthisis bulbi (Fig. 10.39).
3. **Retinitis** characterized by scattered, white, superficial infiltrates may occur during the acute stage of the systemic disease (Fig. 10.40). The lesions are usually transient and heal without scarring.
4. **Retinal vasculitis** may involve both veins (periphlebitis) and arteries (periarteritis) and result in vascular occlusions and macular ischaemia (Fig. 10.41).
5. **Generalized vascular leakage** may give rise to diffuse retinal or optic disc oedema (Fig. 10.42).
6. **Masssive retinal exudation** involving the outer retinal layers, with associated vascular obliteration, is rare but serious (Fig. 10.43).
7. **Vitritis**, which may be severe and persistent, is universal.

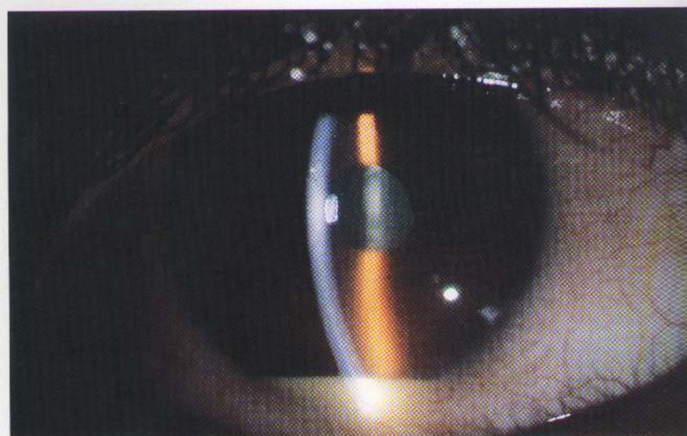


Fig. 10.38
Hypopyon in Behçet disease (Courtesy of B. Noble)

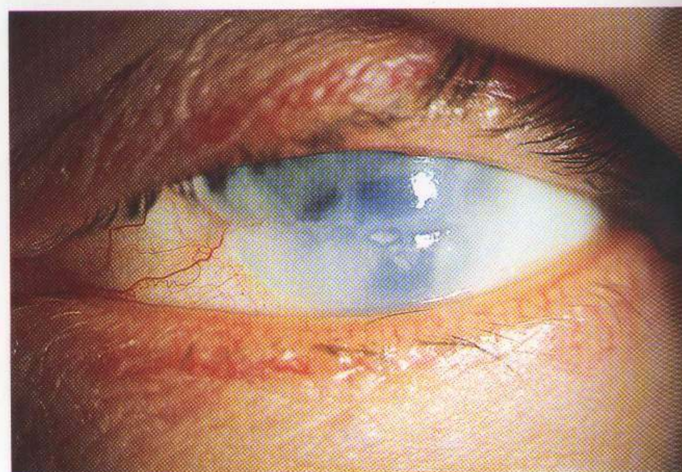


Fig. 10.39
Phthisis bulbi secondary to recurrent anterior uveitis in Behçet disease

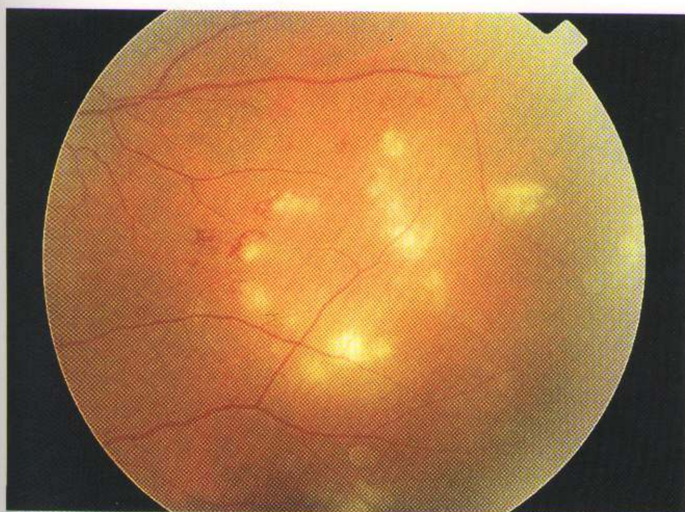


Fig. 10.40
Retinitis in Behçet disease (Courtesy of S. Milewski)

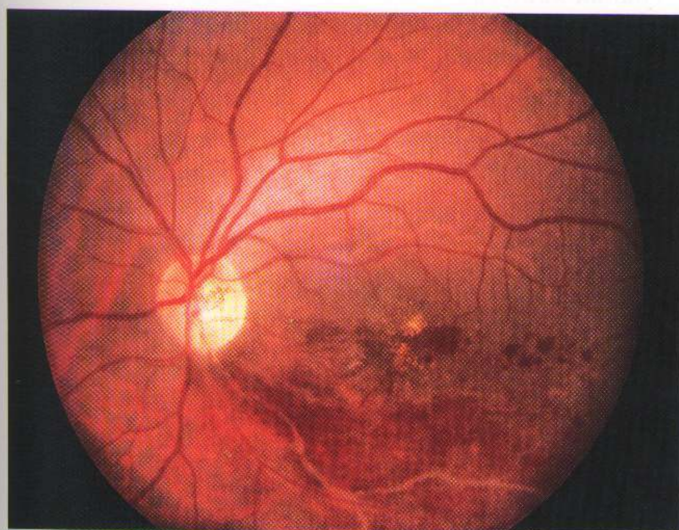


Fig. 10.41
Occlusive retinal vasculitis in Behçet disease

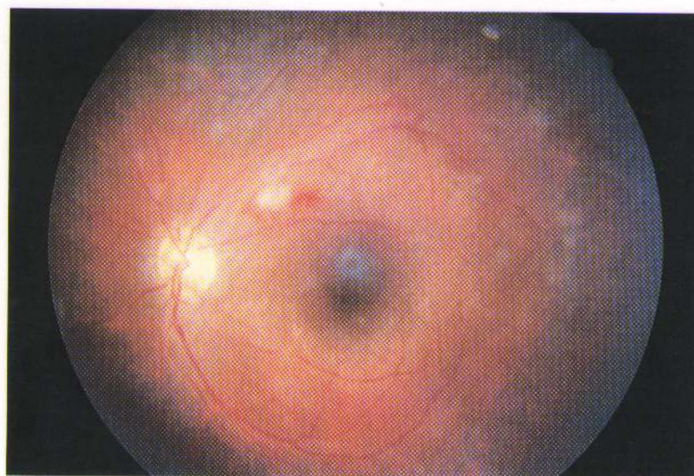


Fig. 10.42
Diffuse retinal oedema in Behçet disease (Courtesy of B. Noble)

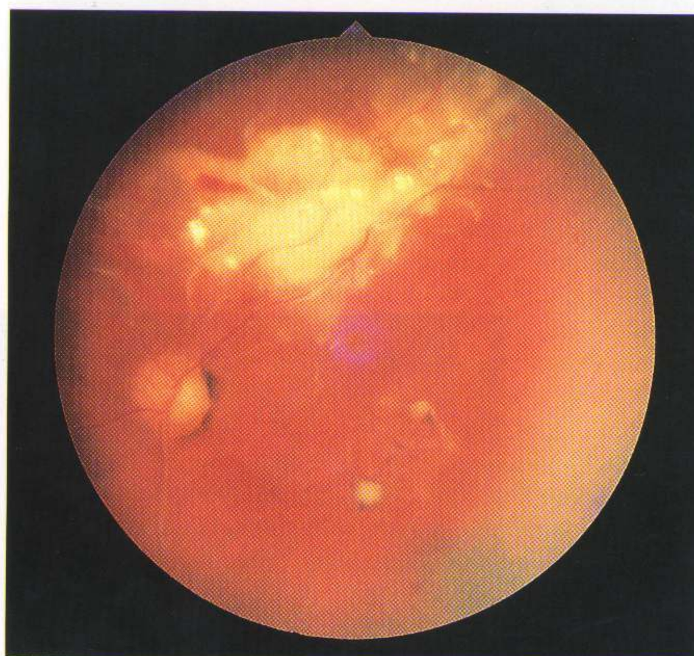


Fig. 10.43
Massive retinal exudation and vascular obliteration in Behçet disease

Treatment of posterior uveitis

Posterior uveitis is treated with high-dose systemic steroids. Unfortunately, the inflammation frequently becomes steroid-resistant and requires alternative therapy with drugs such as cyclosporin, colchicine, azathioprine, chlorambucil and levamisole, which are also useful for the systemic manifestations of the disease. Despite treatment, 5–10% of patients become blind. The end stage of posterior segment involvement is characterized by optic atrophy, vascular attenuation and sheathing, and variable chorioretinal scarring (Fig. 10.44).

> *NB:* A recent study suggests that a single intravenous infusion of infliximab, a drug used for rheumatoid arthritis, is safe and highly effective.

Differential diagnosis

In patients with incomplete or atypical forms of Behçet disease the diagnosis may be uncertain because there are no definitive laboratory tests. It is therefore important to consider the following conditions:

1. **Recurrent anterior uveitis with hypopyon** may be associated with spondylarthropathies. However, such uveitis is not usually simultaneously bilateral. Moreover, the hypopyon is not mobile because it is frequently associated with a fibrinous exudate. In Behçet disease the hypopyon shifts with gravity when head posture changes.
2. **Retinal infiltrates** similar to those in Behçet disease may be seen in viral retinitides such as the acute retinal necrosis syndrome, in which, however, the infiltrates eventually coalesce. Multiple retinal infiltrates also occur in idiopathic acute multifocal retinitis. In contrast to

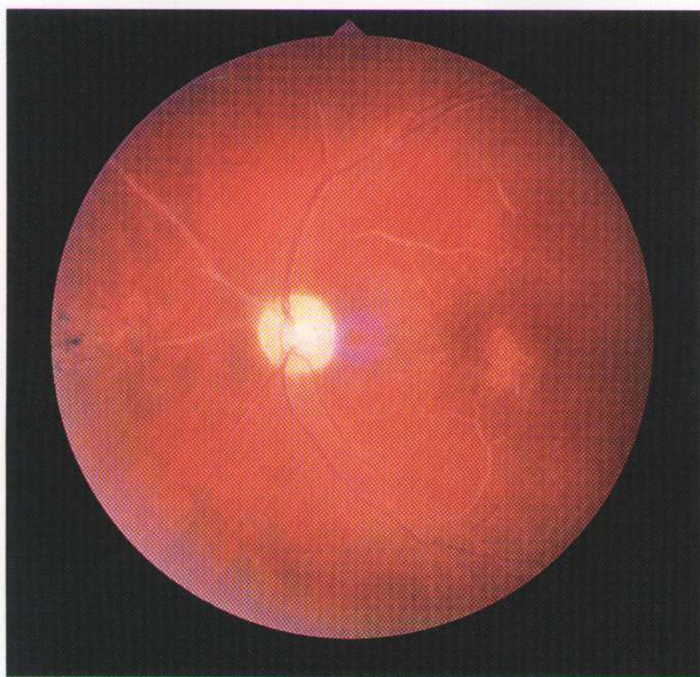


Fig. 10.44
End-stage vascular occlusion, retinal scarring and consecutive optic atrophy in Behçet disease

Behçet disease the clinical course is favourable, with return to normal vision within 2-4 months.

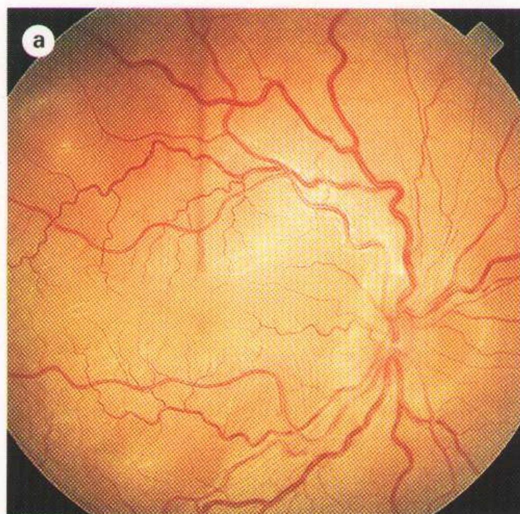
Vogt–Koyanagi–Harada syndrome

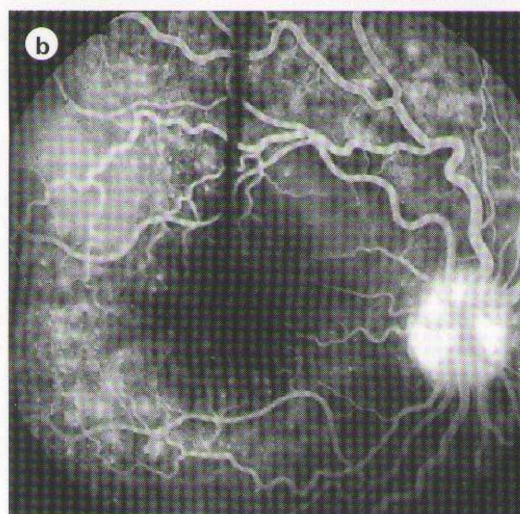
The Vogt–Koyanagi–Harada (V-K-H) syndrome is an idiopathic, bilateral, granulomatous panuveitis associated with systemic manifestations (*see* Chapter 20). In practice, the condition can be subdivided into Vogt–Koyanagi syndrome characterized mainly by cutaneous manifestations and anterior uveitis, and Harada disease, in which neurological features and exudative retinal detachment predominate. V-K-H has three clinical phases: (a) *uveitic*, (b) *convalescent* and (c) *chronic–recurrent.*

Phases

1. Uveitic phase develops within 1–2 days of prodromal manifestations.

*a. **Bilateral anterior uveitis***, usually granulomatous, predominates in Vogt-Koyanagi syndrome and is mild in Harada disease.





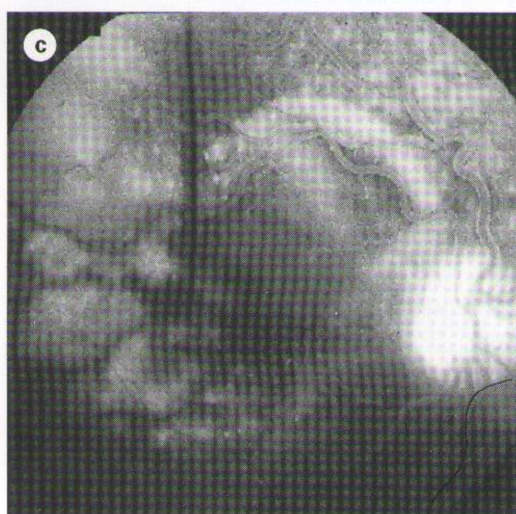
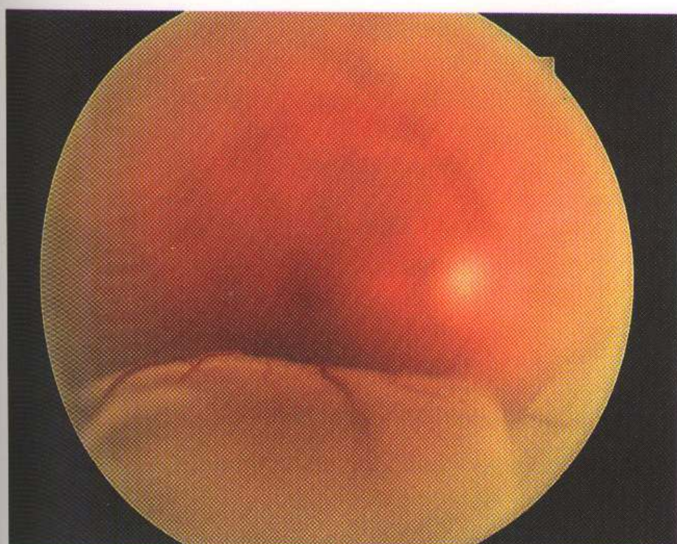
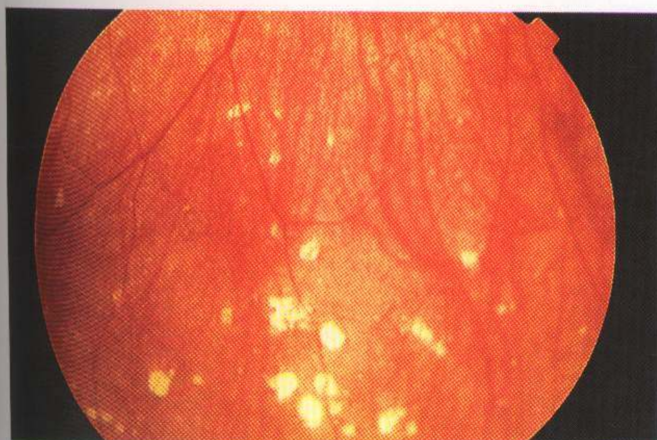


Fig. 10.45
Multifocal detachments of the sensory retina in Harada disease (*see text*) (Courtesy of S. Milewski)


Fig. 10.46
Inferior exudative retinal detachment in Harada disease

*b. **Bilateral posterior uveitis*** occurs in Harada disease and proceeds as follows:
- Optic disc oedema and multifocal detachments of the sensory retina, with small folds radiating from the macula (Fig. 10.45a). FA shows early pinpoint hyperfluorescent spots at the level of the retinal pigment epithelium (Fig. 10.45b), which gradually enlarge as dye pools in the subretinal space (Fig. 10.45c).
- Coalescence of multifocal detachments, resulting in exudative retinal detachment (Fig. 10.46), which gradually subsides spontaneously or with systemic steroid therapy.

2. **Convalescent** phase develops about 4 weeks after the onset of uveitis.
   - Numerous, residual, small, mottled, atrophic scars ('sunset glow' fundus) (Fig. 10.47).
   - Perilimbal vitiligo (Sugiura sign) may be seen, particularly in Japanese patients.
3. **Chronic–recurrent** phase is characterized by chronic granulomatous anterior uveitis, more severe in Vogt–Koyanagi syndrome, often leading to posterior synechiae, secondary cataract and glaucoma.


Fig. 10.47
Chorioretinal scars in Harada disease ('sunset glow' fundus)

Treatment

This is aimed at shortening the duration of the disease and preventing chronicity, with its associated complications. This is best achieved by early and aggressive use of systemic steroids, followed by slow tapering over 3–6 months. Steroid-resistant patients may require cyclosporin, azathioprine or chlorambucil. The prognosis is fair with 60% of patients retaining a visual acuity of at least 6/9. Uncommon posterior segment complications include choroidal neovascularization and rarely subretinal fibrosis.

Viral uveitis

Herpes zoster

The varicella zoster virus (VZV) is a herpes virus that causes chickenpox, remains latent in a primary sensory ganglion, and may subsequently reactivate, resulting in herpes zoster (shingles). Immunosuppressed organ transplant recipients and immune-deficient patients with cancer, leukaemia and AIDS are all at increased risk. In herpes zoster ophthalmicus (HZO), involvement of the tip of the nose (Hutchinson sign), supplied by the external nasal nerve (a terminal branch of the nasociliary nerve), signifies an increased risk of uveitis (Fig. 10.48). Many of the iris changes in patients with uveal involvement are thought to be due to ischaemic occlusive vasculitis.

1. **Presentation** in the vast majority of patients is with HZO, although anterior uveitis may rarely occur in patients with minimal or no cutaneous lesions (herpes zoster sine herpete), the only clue being neuralgia in the distribution of the first division of the trigeminal nerve.


Fig. 10.48
Involvement of the tip of the nose in herpes zoster ophthalmicus (Hutchinson sign)

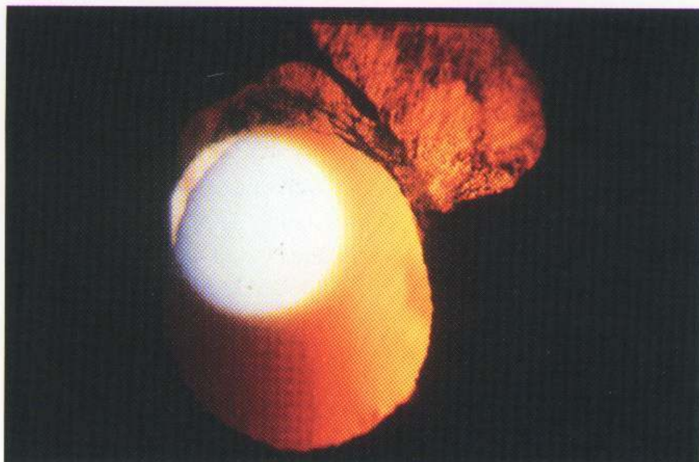


Fig. 10.49
Transillumination defect due to stromal iris atrophy in herpes zoster anterior uveitis

2. **Signs**
   - Corneal sensation may be reduced and nummular keratitis may be present.
   - Keratic precipitates are frequently small and occasionally 'mutton fat'.
   - Anterior chamber activity is usually mild.
   - Iridoplegia and sectoral iris oedema.
   - Posterior synechiae are common.
3. **Complications** may occur if the uveitis is not treated vigorously.
   a. Iris atrophy is characterized by sectoral loss of the iris pigment epithelium, due to ischaemic vasculitis, resulting in transillumination defects (Fig. 10.49).
   b. Secondary glaucoma, often acute, occurs in about 10% of eyes, due to combination of trabecular inflammation (trabeculitis) and obstruction by inflammatory debris.
4. **Treatment** with topical steroids needs to be continued for several months and then tapered very gradually. Some patients may require very low-dose treatment indefinitely in order to maintain long-term control of the inflammation.

NB: Although the diagnosis is usually straightforward, it is important to remember that severe uveitis may follow an almost inapparent episode of herpes zoster. The initial diagnosis may well have been missed and the patient may present months later with a florid unilateral anterior uveitis. It is therefore important always to consider the possibility of HZO and perform the following:
- Test corneal sensation because it is often reduced after HZO.
- Examine the cornea for nummular keratitis.
- Transilluminate the iris for sectoral atrophy.
- Inspect the hairline at the scalp for post-herpetic scarring and pigmentary changes.

Cytomegalovirus retinitis

Cytomegalovirus (CMV) retinitis is the most common ocular infection in AIDS patients and on rare occasions may be the initial manifestation of the disease (*see* Chapter 20). Before the advent of highly active antiretroviral therapy (HAART), CMV retinitis affected 30% of patients with AIDS at some time during the course of their disease. Since the introduction of HAART the incidence of CMV retinitis has substantially decreased.

Clinical features

1. **Indolent retinitis** frequently starts in the periphery and progresses slowly. It is characterized by mild granular opacification (Fig. 10.50).
2. **Fulminating retinitis** (in chronological order)
   - Dense, white, geographical area of opacification associated with vasculitis and mild vitritis (Fig. 10.51).
   - Gradual spread associated with haemorrhage (Fig. 10.52).

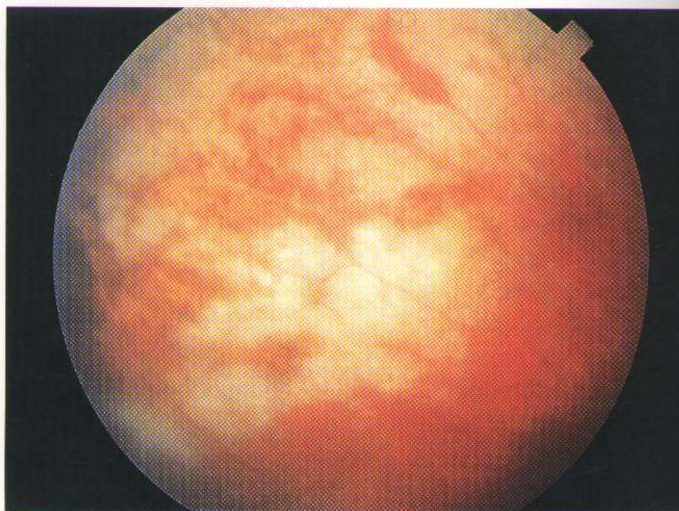


Fig. 10.50
Indolent CMV retinitis

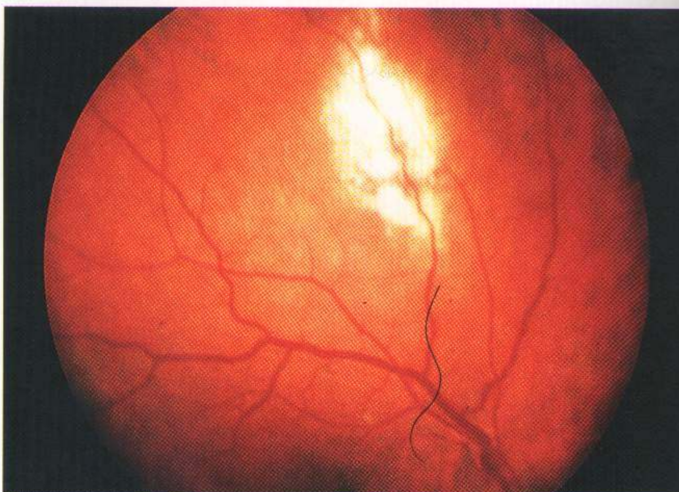


Fig. 10.51
Early fulminating CMV retinitis

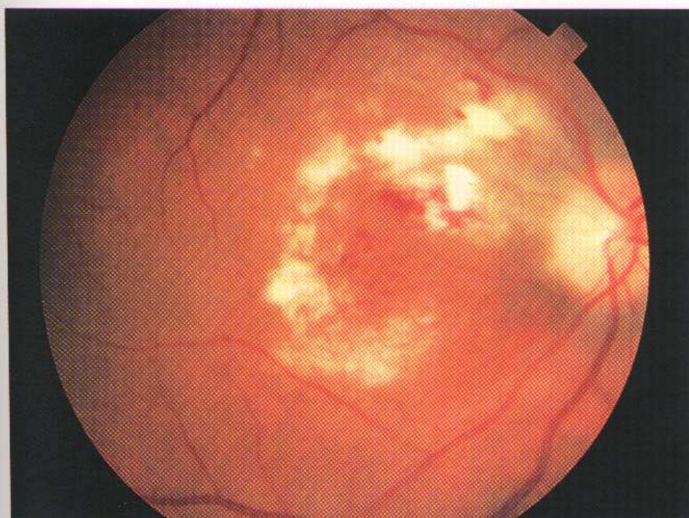


Fig. 10.52
Fulminating CMV retinitis

- Slow but relentless 'brushfire-like' extension along the retinal blood vessels (Fig. 10.53) and involvement of the optic nerve head (Fig. 10.54).
- Without treatment blindness ensues within several weeks to a few months from extensive retinal involvement (Fig. 10.55), retinal detachment or consecutive optic atrophy.

3. **Regression** following treatment is characterized by fewer haemorrhages, less opacification, and diffuse atrophic and pigmentary changes (Fig. 10.56).

Treatment

Retinal detachment is frequently amenable to vitrectomy and silicone oil tamponade. The following drugs may be used individually or in combination to treat active CMV.

1. **Systemic ganciclovir** is initially administered intravenously, 10 mg/kg every 12 hours for 2–3 weeks (induction), and subsequently at 5 mg/kg every 24 hours until

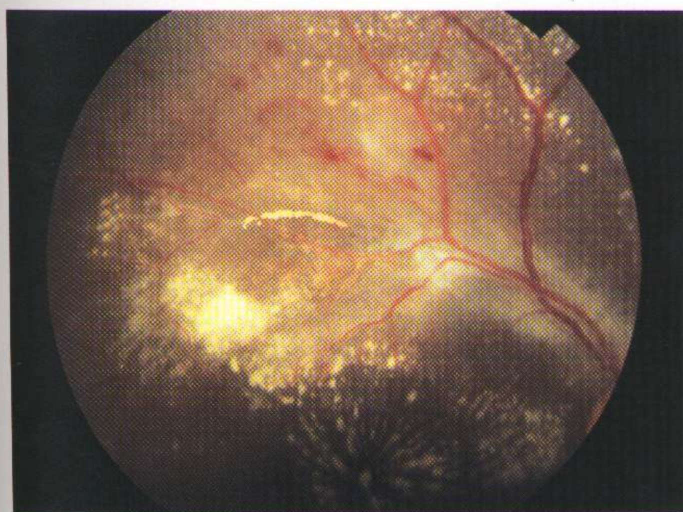


Fig. 10.53
Fulminating CMV retinitis (Courtesy of S. Milewski)

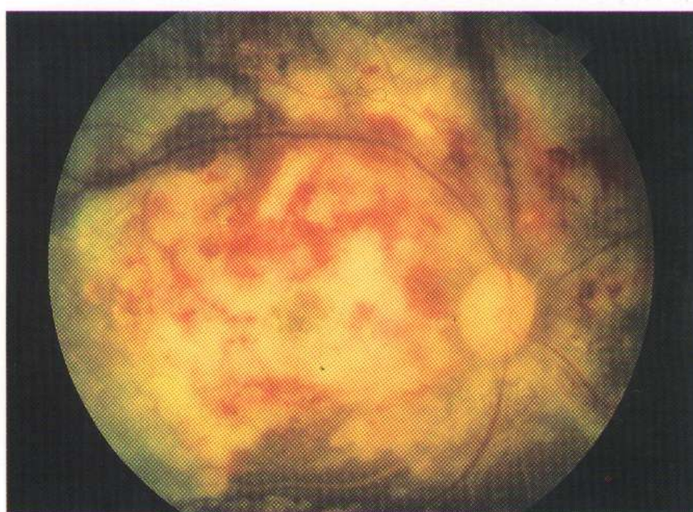


Fig. 10.55
End-stage CMV retinitis

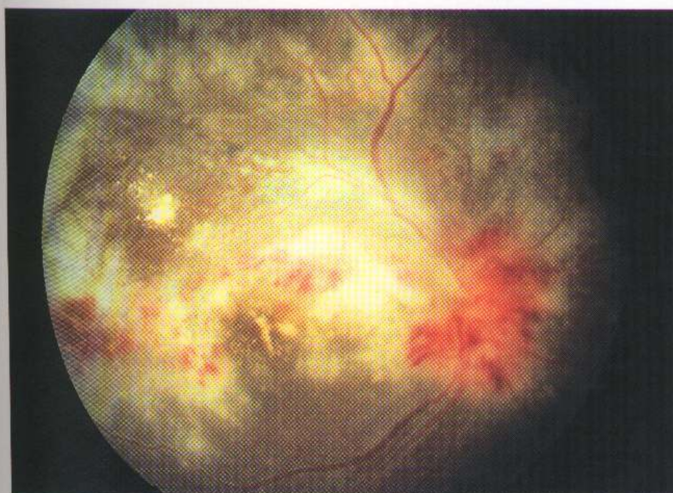


Fig. 10.54
Optic nerve head involvement by fulminating CMV retinitis (Courtesy of S. Milewski)

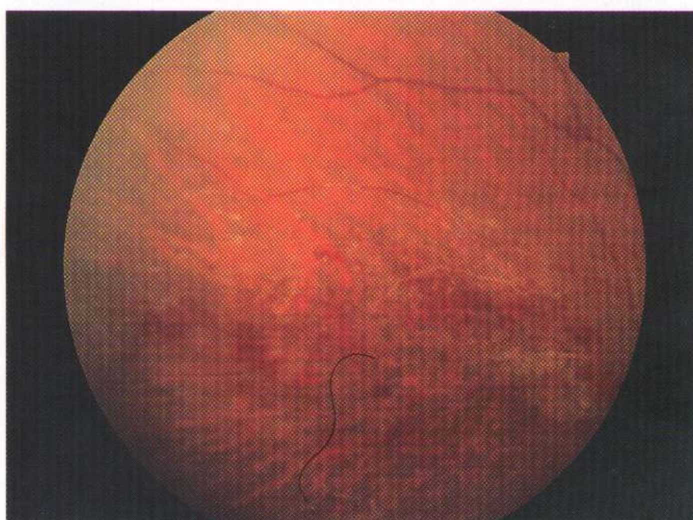


Fig. 10.56
Inactive CMV retinitis

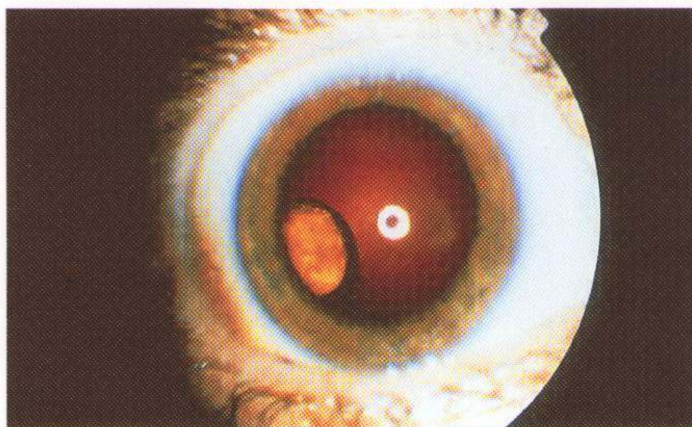


Fig. 10.57
Slow-release intravitreal ganciclovir implant (Courtesy of V. Tanner)

retinitis is stable. Thereafter the lifelong oral maintenance dose is 300 mg daily. Ganciclovir is effective in 80% of patients but half of these subsequently relapse and require reinduction. The drug carries a high risk of bone marrow suppression, which often forces interruption of treatment.

2. **Intravitreal ganciclovir**, by injection or a slow-release device (Vitrasert, duration of action 8 months) (Fig. 10.57), is as effective as intravenous therapy. However, this fails to protect the fellow eye and is less effective in treating recurrences in patients previously treated with intravenous ganciclovir. Intravitreal injections may also cause serious complications such as vitreous haemorrhage, retinal detachment and endophthalmitis.
3. **Foscarnet** administered intravenously, 60 mg/kg every 8 hours for 2–3 weeks and then daily, is an alternative to ganciclovir. Side effects include nephrotoxicity, electrolyte disturbances and seizures. Foscarnet can also be given intravitreally.
4. **Cidofovir** administered intravenously, 5 mg/kg once weekly for 2 weeks and then every 2 weeks, in combination with probenecid, may be used where other agents are unsuitable. Side effects include nephrotoxicity, neutropenia and uveitis. Cidofovir can also be given intravitreally.

Prognosis

With treatment there is an initial 95% response but relapse is invariable within 2 weeks if treatment is discontinued. The relapse rate within 6 months in patients on maintenance therapy is 50%. Patients who demonstrate a sustained HAART-induced immune recovery with elevation of CD4+ cell count are more likely to remain quiescent for a longer period of time if anti-CMV therapy is withdrawn. However, such patients may develop transient but severe vitreous inflammation which probably reflects an improved anti-CMV immune response.

Other types of uveitis in AIDS

The following types of uveitis may occur in AIDS in the absence of opportunistic infections:

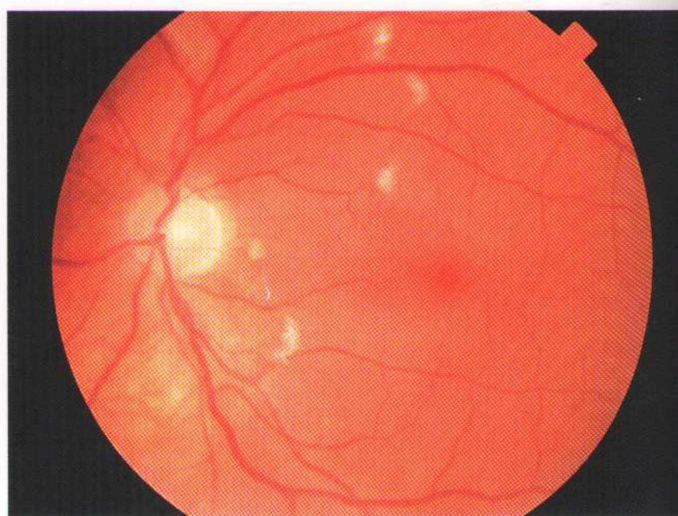


Fig. 10.58
Cotton wool spots in HIV retinopathy (Courtesy of S. Milewski)

1. **HIV-induced** retinal microangiopathy is characterized by multiple, usually asymptomatic cotton wool spots (Fig. 10.58) which resolve spontaneously.
2. **Cidofovir-induced** uveitis responds well to conventional treatment with topical steroids and may not preclude continuation of cidofovir.
3. **Rifabutin-induced** uveitis in patients treated for *Mycobacterium avium* complex infections.
4. **Immune recovery** uveitis is a paradoxical worsening of intraocular inflammation, mainly vitritis, in patients with HAART-induced immune recovery who also have inactive CMV retinitis. Complications include cataract, cystoid macular oedema and epiretinal gliosis.
5. **Chronic multifocal retinal infiltrates** associated with anterior uveitis or vitritis are rare. The uveitis responds well to steroids and the retinitis to zidovudine. Visual prognosis is good.

Progressive outer retinal necrosis

Progressive outer retinal necrosis (PORN) is a devastating condition caused by an aggressive variant of varicella zoster virus and is the second most common opportunistic retinal infection in AIDS.

1. **Presentation** is with rapidly progressive visual loss which is often initially unilateral and then becomes bilateral.
2. **Signs** (in chronological order)
   - Multifocal, deep, yellow-white, retinal infiltrates with minimal vitritis.
   - Rapid confluence, full-thickness retinal necrosis and early macular involvement (Fig. 10.59).
3. **Investigations**. Specific PCR-based diagnostic assay for varicella zoster virus DNA may be performed on vitreous samples to confirm the diagnosis.
4. **Treatment** is with intravenous ganciclovir alone or in combination with foscarnet. Despite treatment, most patients become blind in both eyes within a few weeks as a

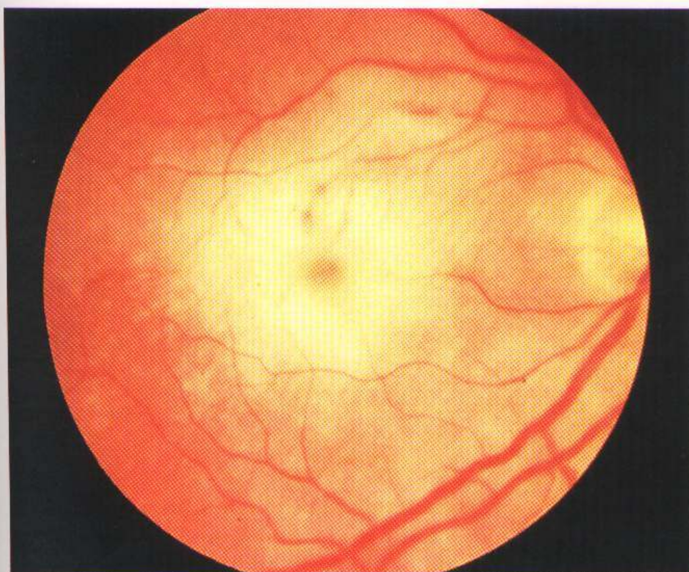


Fig. 10.59
Macular involvement in progressive outer retinal necrosis
(Courtesy of S. Mitchell)

result of macular necrosis or retinal detachment. In addition 50% are dead 5 months after the diagnosis. The results of retinal surgery are disappointing, although vitrectomy with silicone oil tamponade and relaxing retinotomy may salvage ambulatory vision in a few cases.

Acute retinal necrosis

Acute retinal necrosis (ARN) is a rare but devastating necrotizing retinitis, typically affecting otherwise healthy individuals of all ages. The aetiology is biphasic: due to herpes simplex virus 2 under the age of 15 years and to varicella zoster virus and herpes simplex virus 1 in older individuals. It is twice as common in males.

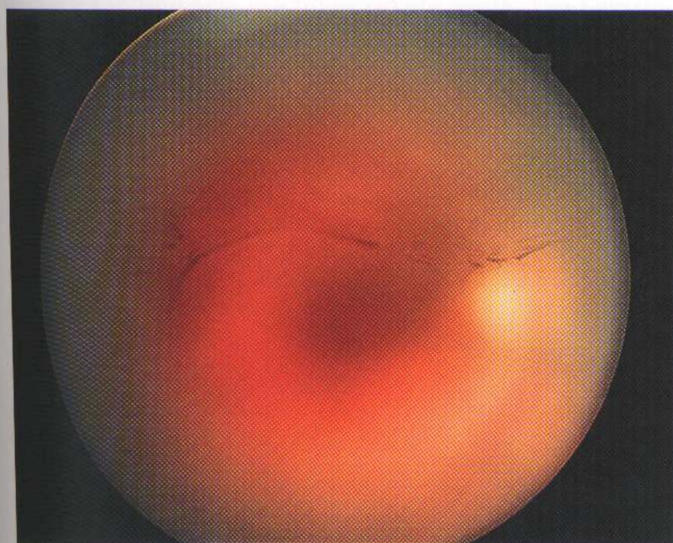


Fig. 10.60
Vitritis in acute retinal necrosis

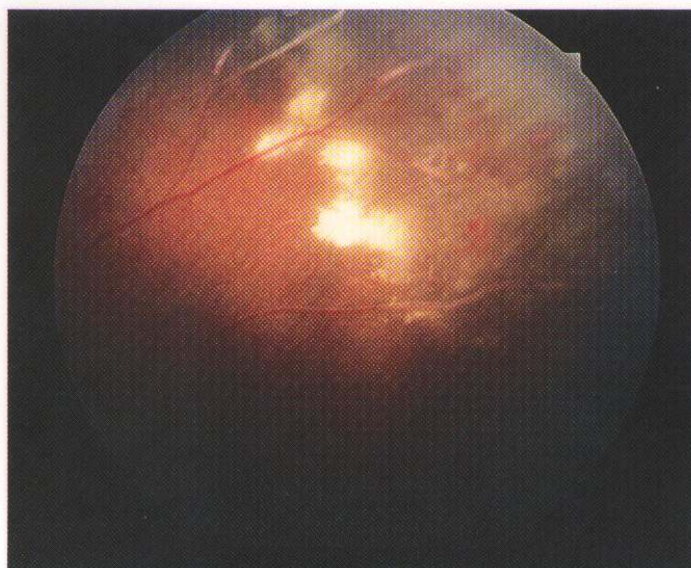


Fig. 10.61
Early acute retinal necrosis

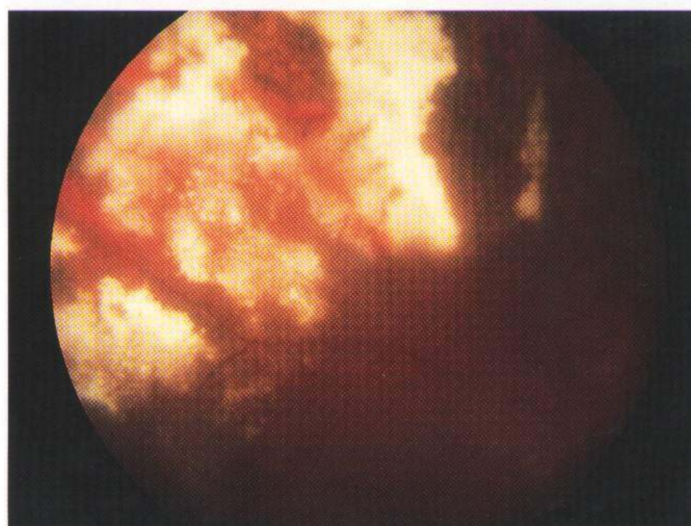


Fig. 10.62
Advanced acute retinal necrosis

Clinical features

1. **Presentation** is variable. Some patients develop painful severe visual impairment over a few days, while others have an insidious onset with mild visual symptoms such as floaters.
2. **Signs** (in chronological order)
   - Anterior granulomatous uveitis and vitritis (Fig. 10.60) are universal; unless the fundus is examined the diagnosis may be missed.
   - Peripheral retinal periarteritis and multifocal, deep, yellow-white, retinal infiltrates (Fig. 10.61).
   - Gradual confluence of the lesions (Fig. 10.62) and the development of full-thickness retinal necrosis.

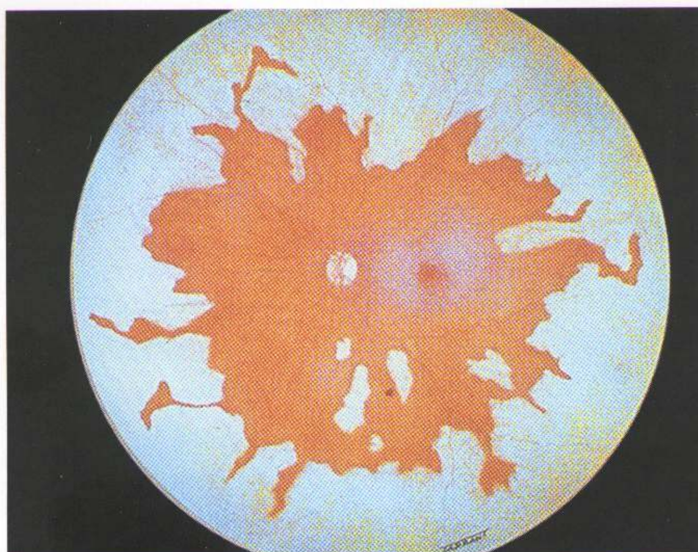


Fig. 10.63
Advanced acute retinal necrosis

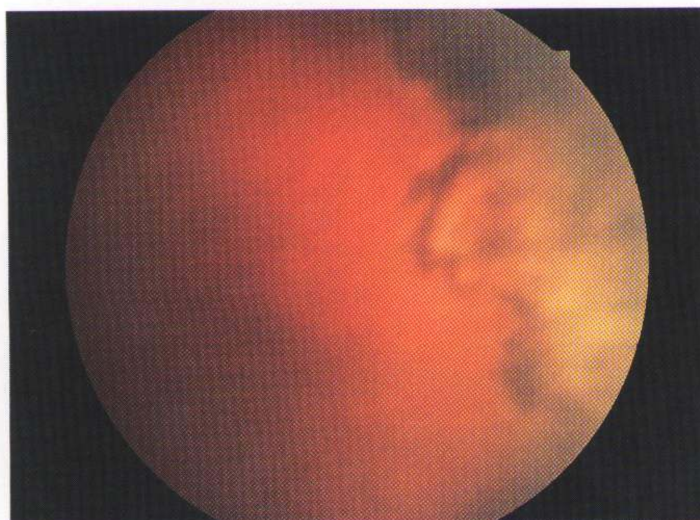


Fig. 10.64
Resolved acute retinal necrosis

- The posterior pole is usually spared until late. Visual acuity may therefore remain fairly good despite necrosis of the surrounding retina (Fig. 10.63).
- Other signs include optic disc oedema, choroidal thickening and retinal haemorrhages.

3. **Investigations**. PCR-based assays of aqueous and vitreous are very helpful in confirming the diagnosis and determination of the causative virus.
4. **Course**. The retinitis resolves within 6–12 weeks, leaving behind necrotic retina with hyperpigmented borders (Fig. 10.64). Without appropriate treatment the second eye becomes involved in about 65% of cases, usually within 6–14 weeks of the first. The prognosis with treatment is guarded, with a final visual acuity of 6/12 or better in 50% of cases. Complications include retinal detachment, which may be rhegmatogenous or tractional, anterior ischaemic optic neuropathy and retinal vascular occlusion.

Treatment

1. **Aciclovir** initially intravenously for 14 days (10 mg kg per day in three divided doses) and then orally for 3 months (800 mg five times daily). There may be no signs of improvement for up to 5 days after starting therapy. Treatment also reduces but does not eliminate the risk of fellow eye involvement.
2. **Famciclovir** orally 500 mg t.i.d. for 3 months may be helpful in patients unresponsive to aciclovir.
3. **Systemic steroids** are started a few days after initiation of antiviral therapy.
4. **Aspirin** may be used in an effort to prevent vascular obstructive complications.
5. **Prophylactic** argon laser photocoagulation, to create a chorioretinal adhesion in areas of potential retinal break formation, may be effective in preventing retinal detachment if applied early.
6. **Vitreoretinal surgery**, including silicone oil tamponade, may be successful for complicated retinal detachments.

Congenital rubella

Rubella (German measles) is a benign febrile exanthema. Congenital rubella results from transplacental transmission of virus to the fetus from an infected mother, usually during the first trimester of pregnancy, resulting in serious chronic fetal infection and malformations. The risk to the fetus is related to the stage of gestation at the time of maternal infection, being highest in the first 8 weeks of pregnancy. In order of frequency, ocular complications are as follows:

1. **Retinopathy** is characterized by a visually insignificant, subtle 'salt and pepper' pigmentary disturbance, most marked at the macula (Fig. 10.65). A small percentage of cases may later develop choroidal neovascularization.
2. **Pearly nuclear cataract** may be unilateral or bilateral. Cataract surgery may be associated with a florid intractable uveitis.

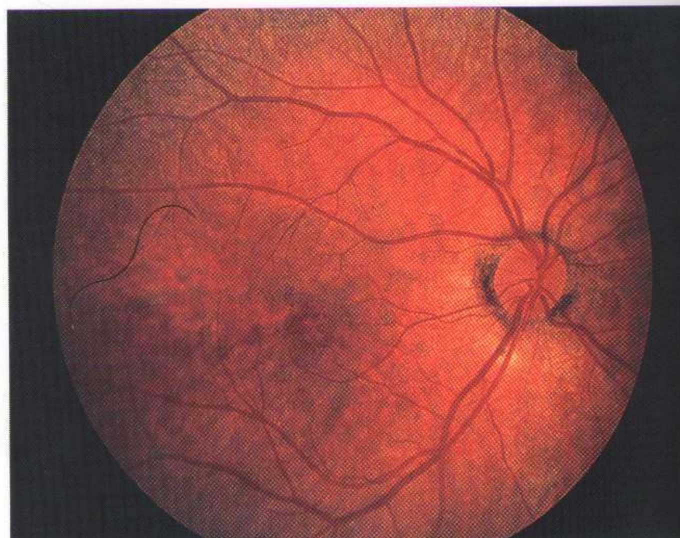


Fig. 10.65
Rubella retinopathy



Fig. 10.66
Left microphthalmos in rubella

3. **Microphthalmos** (Fig. 10.66) is often associated with cataracts, optic nerve abnormalities and glaucoma.
4. **Glaucoma** develops usually during the neonatal period, resulting in buphthalmos. However, in a microphthalmic eye, the raised intraocular pressure may enlarge the cornea to normal size. Corneal oedema is also an important feature of glaucoma.
5. **Miscellaneous** complications include stromal keratopathy, iritis, iris atrophy and extreme refractive errors. Pendular nystagmus and strabismus may develop as a consequence of the various ocular abnormalities.

Parasitic uveitis

Toxoplasma retinitis

Toxoplasma gondii is an obligate intracellular protozoan. The cat is the definitive host and other animals, such as mice, livestock and humans, are intermediate hosts. The parasite has three forms: (a) *sporocysts* (oocysts), which are excreted in cat faeces, (b) *bradyzoites*, which are encysted in tissue, and (c) *tachyzoites*, which proliferate and cause tissue destruction. Toxoplasmosis is the most frequent cause of infectious retinitis in immunocompetent individuals. Although most cases are thought to represent reactivation of prenatal infestation it is likely that postnatally acquired toxoplasma retinitis may be more frequent than previously realized. Recurrent episodes, usually between the ages of 10 and 35 years, are common and occur when the cysts rupture, releasing hundreds of tachyzoites into adjacent normal retinal cells. The scars from which recurrences arise may be the residue of previous congenital infestation or, less frequently, remote acquired involvement. Active retinitis is usually associated with anterior uveitis which may be non-granulomatous or granulomatous. It is therefore very important to examine the fundus in all patients with anterior uveitis.

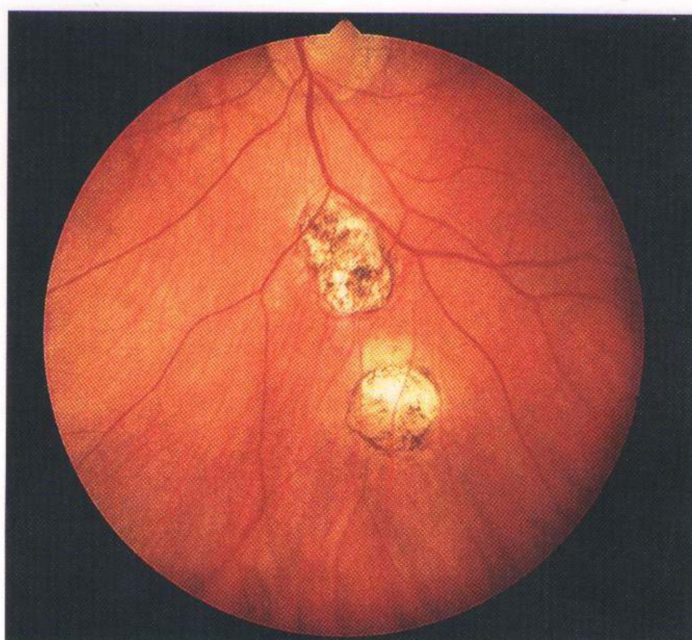


Fig. 10.67
Peripheral chorioretinal scars due to toxoplasmosis

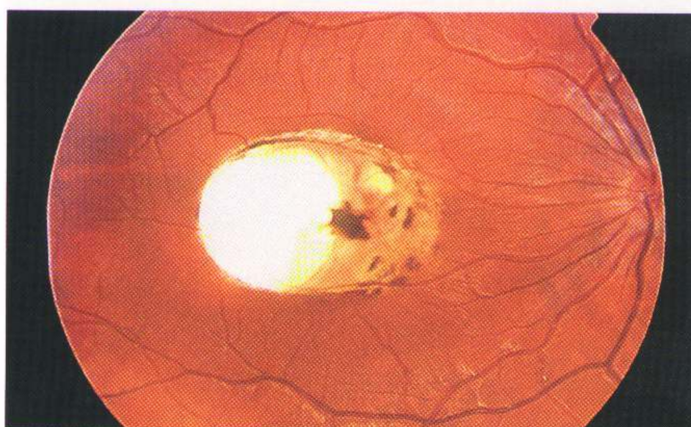


Fig. 10.68
Macular scarring due to toxoplasmosis

Signs

1. **Quiescent** healed lesions are foci of chorioretinal atrophy and scarring, with pigmented borders (Fig. 10.67). They are often bilateral and often discovered incidentally, or when a child is noted to have impaired vision because of macular involvement (Fig. 10.68).
2. **Focal retinitis**
   - A solitary inflammatory focus of variable size, with overlying vitreous haze, adjacent to an old pigmented scar ('satellite lesion') is the most common finding (Fig. 10.69).
   - Severe vitritis may impair visualization of the fundus, although the inflammatory focus may still be discernible ('headlight in the fog' appearance) (Fig. 10.70).
   - Associated features include vasculitis and in some cases the detached posterior hyaloid face becomes covered by inflammatory precipitates.

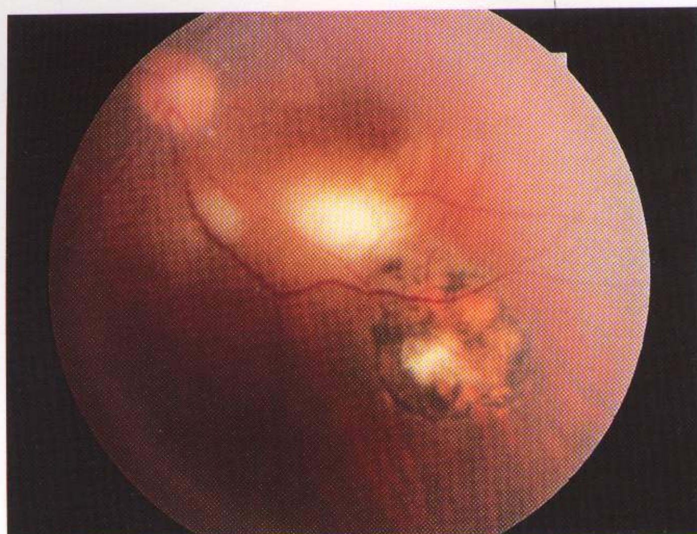


Fig. 10.69
Typical toxoplasma retinitis

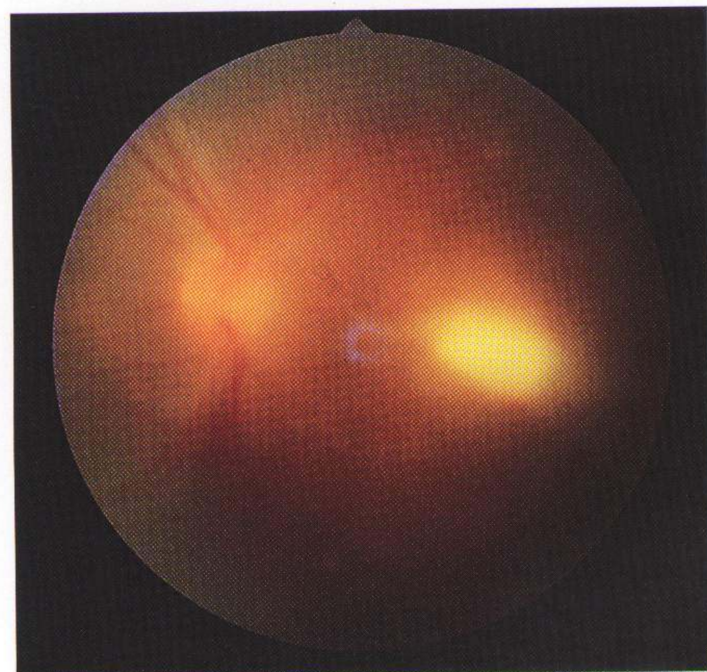


Fig. 10.70
Toxoplasma retinitis and severe vitritis resulting in a 'headlight in the fog' appearance

3. **Papillitis** (inflammation of the optic nerve head) may be secondary to juxtapapillary retinitis (Jensen choroiditis) (Fig. 10.71). Very occasionally, the optic nerve head may be the primary site of involvement.
4. **Atypical lesions**, which may occur in immunocompromised individuals, are characterized by bilateral, multifocal, discrete foci (Fig. 10.72) or extensive confluent areas of retinitis (Fig. 10.73). Pre-existing scars are absent, implying that the infestation has been newly acquired or disseminated to the eye from extraocular sites.

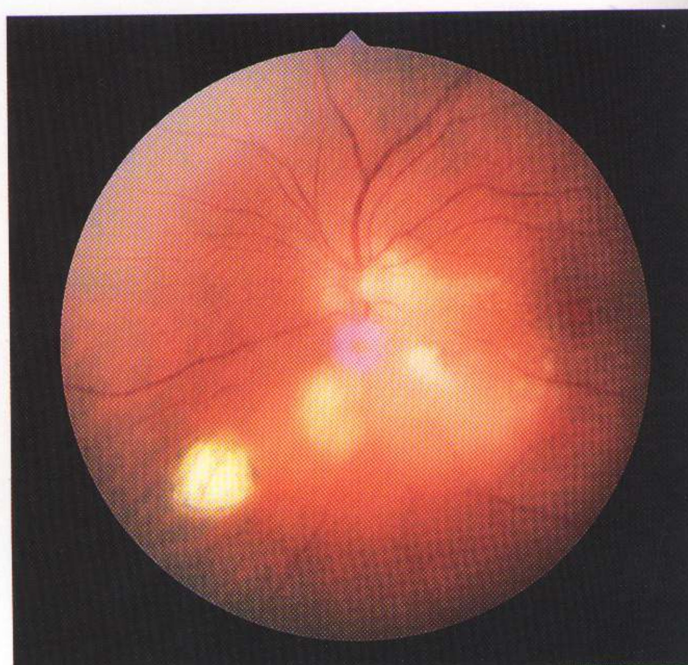


Fig. 10.71
Juxtapapillary toxoplasma retinitis

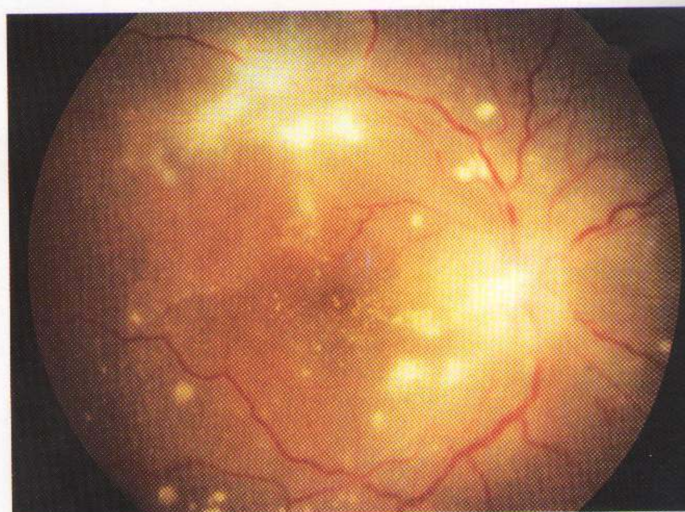


Fig. 10.72
Atypical multifocal toxoplasma retinitis in AIDS (Courtesy of J. Salmon)

Diagnostic tests

Diagnosis is based on a compatible fundus lesion and positive serology for toxoplasma antibodies. Any antibody titre is significant, there being no correlation between titre and inflammatory activity.

1. **Indirect immunofluorescent antibody** tests utilize dead organisms that are exposed to the patient's serum and anti-human globulin labelled with fluorescein. The results are interpreted under fluorescent microscopy.
2. **Haemagglutination** tests involve coating of lysed organisms on to red blood cells, which are then exposed to the patient's serum. Positive sera cause the red cells to agglutinate.

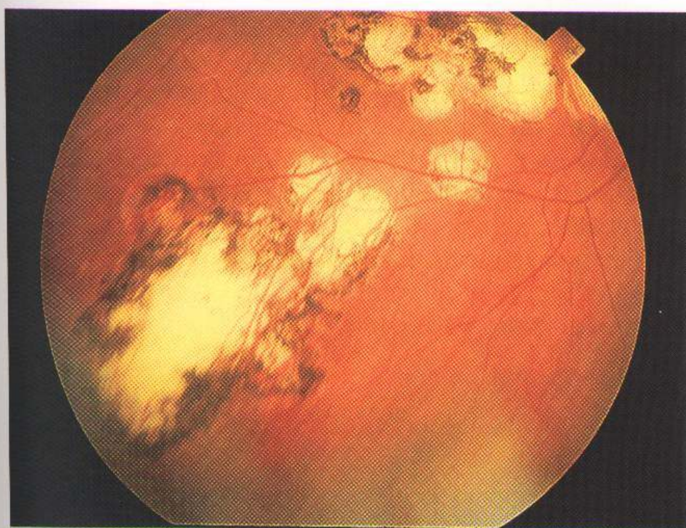


Fig. 10.73
Confluent scarring due to toxoplasmosis

3. **Enzyme-linked immunosorbent assay** (ELISA) involves binding of the patient's serum to an excess of solid-phase antigen. This complex is then incubated with an enzyme-linked second anti-human antibody. Assessment of enzyme activity provides a measure of specific antibody concentration. The test can also detect antibodies in the aqueous humour, which are more specific than those in the serum.

Indications for treatment

1. **In immunocompetent** patients not all active lesions require treatment; small peripheral foci are frequently self-limiting and innocuous. The following are the main indications for treatment:



Fig. 10.74
Toxoplasma retinitis involving the papillomacular bundle
(Courtesy of M. Szreter)

   - A lesion threatening or involving the macula, papillomacular bundle (Fig. 10.74), optic nerve head or a major blood vessel.
   - A very severe vitritis, due to the risk of subsequent vitreous fibrosis and tractional retinal detachment.
2. **In immunocompromised** patients all lesions should be treated irrespective of location or severity.

Treatment

There is no universally agreed therapeutic regimen. Treatment influences neither the duration of inflammation nor the frequency of recurrences, although it appears to limit the ultimate size of the scar. Systemic steroids are indicated for vision-threatening lesions, particularly if associated with severe vitritis, and are administered in conjunction with one or more of the following agents. Steroids are, however, contraindicated in immunocompromised patients.

1. **Clindamycin** 300 mg q.i.d. orally for 3 weeks. If used alone, it may cause a pseudomembranous colitis. The risk of colitis is reduced when clindamycin is used together with sulphadiazine that inhibits clostridial overgrowth.
2. **Sulphadiazine**. The loading oral dose is 2 g followed by 1 g q.i.d. for 3–4 weeks. Side effects include renal stones, allergic reactions and Stevens–Johnson syndrome.
3. **Pyrimethamine** (Daraprim) is a strong anti-toxoplasma agent, which may, however, cause thrombocytopenia, leucopenia and folate deficiency. For this reason, weekly blood counts should be done and the drug used only in combination with oral folinic acid 4 mg three times a week (mixed with orange juice) to counteract side effects. The loading dose is 50 mg followed by 25–50 mg daily for 4 weeks. Pyrimethamine should not be used in patients with AIDS.
4. **Co-trimoxazole** (Septrin) (trimethoprim 160 mg and sulphamethoxazole 800 mg) 960 mg b.d. orally for 4–6 weeks, may be effective alone or in combination with clindamycin.
5. **Atovaquone** 750 mg t.i.d. has been used mainly for pneumocystosis and toxoplasmosis in AIDS but may also be effective against toxoplasma retinitis in immunocompetent individuals. The drug is relatively free of serious side effects but is expensive.
6. **Azithromycin** 500 mg daily on three successive days may be used in patients intolerant to other drugs.

Prognosis

In immunocompetent hosts, the retinitis heals within 1–4 months. The vitreous haze gradually clears although some condensation may remain. The inflammatory focus evolves into a sharply demarcated atrophic scar with a hyperpigmented border (*see* Fig. 10.67). Resolution of anterior uveitis is a reliable sign of posterior segment healing. After the first attack, the mean recurrence rate within 3 years is about 50% and the average number of recurrent attacks per patient is 2.7. Eyes with toxoplasmosis may lose vision from direct or indirect causes:

1. **Direct involvement** by an inflammatory focus of the fovea, papillomacular bundle, optic nerve head or a major blood vessel.
2. **Indirect involvement** by macular pucker or retinal detachment (tractional or rhegmatogenous).

Toxocariasis

Toxocariasis is caused by infestation with *Toxocara canis*, a common intestinal roundworm of dogs. Human infestation occurs secondary to ingestion of soil or food contaminated with ova shed in dogs' faeces. In the intestine, the ova develop into larvae, which penetrate the intestinal wall and travel to various organs such as the liver, lungs, skin, brain and eyes. When the larvae die, they disintegrate and cause an inflammatory reaction followed by granulation. Clinically human infestation may take one of two forms (a) *visceral larva migrans* and (b) *ocular toxocariasis*.

Unlike visceral larva migrans, which is a severe systemic infestation usually occurring around the age of 2 years, in which the eyes are spared, ocular toxocariasis occurs in otherwise healthy children. It may take one of three forms, all affecting only one eye: (a) *a chronic endophthalmitis-like picture*, (b) *posterior pole granuloma* and (c) *peripheral granuloma*. Of these, only the first is associated with active inflammation. Less common manifestations include anterior uveitis, papillitis, a localized vitreous abscess and retinal tracks.

Chronic endophthalmitis

1. **Presentation** is between 2 and 9 years of age with leukocoria, strabismus or unilateral visual loss.
2. **Signs**. Anterior uveitis and vitritis. The peripheral retina and pars plana may be covered by a dense greyish-white exudate, similar to 'snow-banking' in pars planitis (Fig. 10.75).
3. **Complications** include tractional retinal detachment, hypotony and cataract.
4. **Treatment** with periocular steroids may be helpful. Vitreoretinal surgery may be beneficial for tractional retinal detachment but in general the prognosis is very poor; some eyes eventually require enucleation.

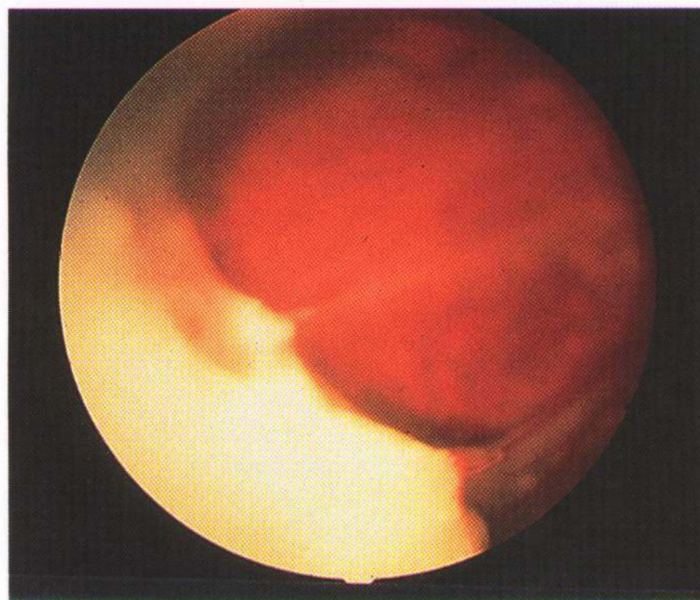


Fig. 10.75
Peripheral exudation in chronic toxocara endophthalmitis
(Courtesy of S. Lightman)

Posterior pole granuloma

1. **Presentation** is between 6 and 14 years of age with unilateral visual impairment.

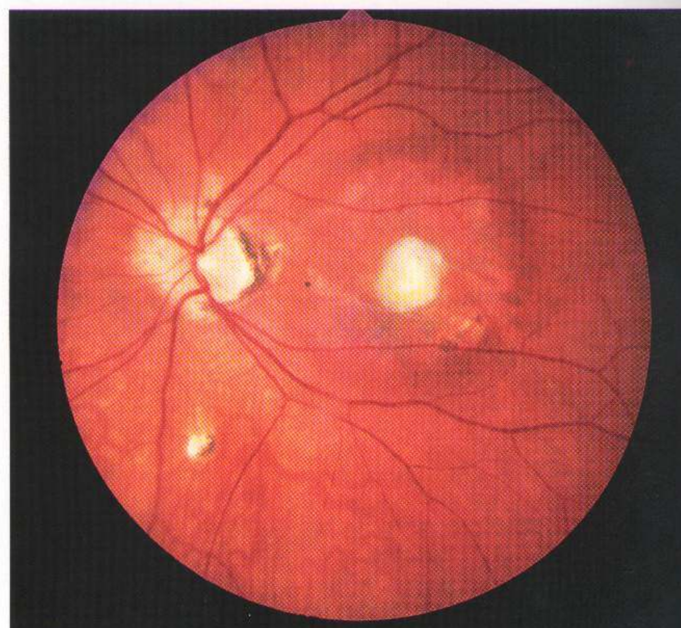


Fig. 10.76
Toxocara granuloma at the posterior pole

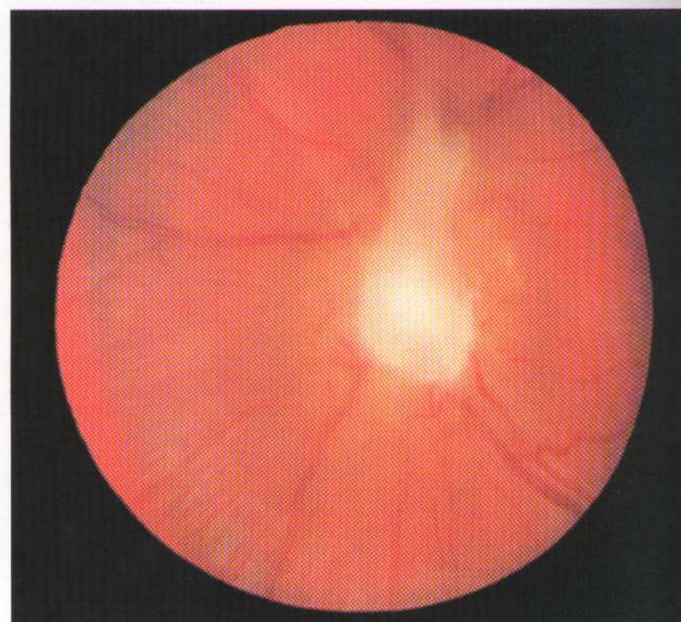


Fig. 10.77
Toxocara granuloma involving the optic nerve head

2. **Signs**. Absence of uveitis. A round, yellow-white, solid granuloma between one to two discs in diameter, is seen at the macula (Fig. 10.76). Occasionally it may involve the optic nerve head (Fig. 10.77).
3. **Complications** include retinal stress lines, vascular distortion, hard exudates surrounding the lesion, subretinal haemorrhage and retinal detachment (Fig. 10.78), which may be amenable to vitreoretinal surgery.

Peripheral granuloma

1. **Presentation** is usually during adolescence or adult life with visual impairment from distortion of the macula or retinal detachment. In an uncomplicated case, the lesion may remain undetected throughout life.

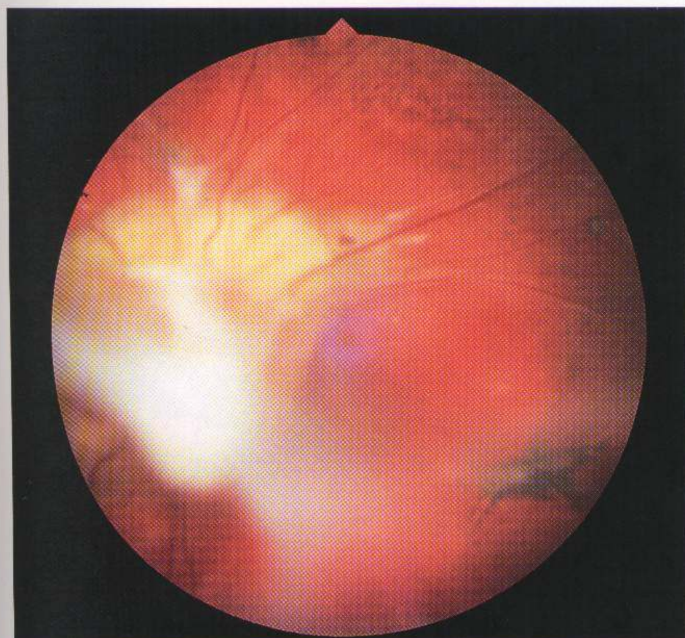


Fig. 10.78
Tractional retinal detachment due to a toxocara granuloma

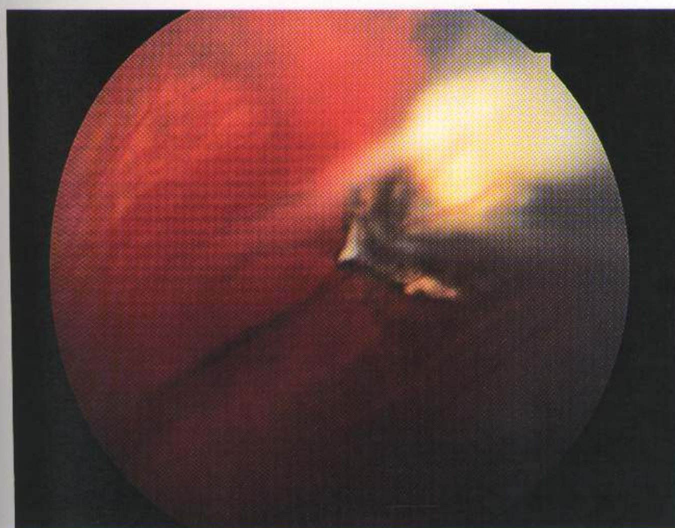


Fig. 10.79
Peripheral toxocara granuloma

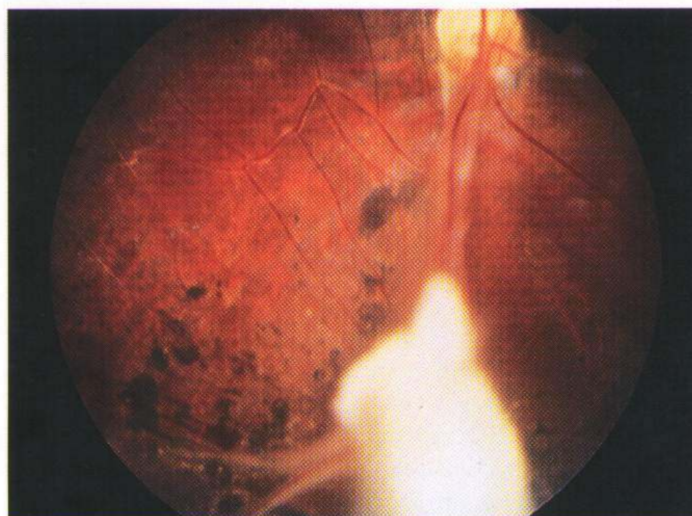


Fig. 10.80
Peripheral toxocara granuloma with vitreous bands (Courtesy of K. Rahman)

2. **Signs**. Absence of uveitis. A white hemispherical granuloma may be seen at or anterior to the equator in any quadrant of the fundus (Fig. 10.79). Vitreous bands frequently extend from the lesion to the posterior fundus; on contraction they may give rise to 'dragging' of the disc and straightening of blood vessels (Fig. 10.80).
3. **Complications** include macular heterotopia (abnormal position), which may result in pseudo-strabismus, and tractional retinal detachment, which may be amenable to vitreoretinal surgery.

Diagnostic tests

1. **ELISA** can be used to determine the level of serum antibodies to *Toxocara canis*. When ocular toxocariasis is suspected, exact ELISA titres should be requested, including testing of undiluted serum. Any positive titre is consistent with, but not necessarily diagnostic of, toxocariasis. It must therefore be interpreted in conjunction with the clinical findings. A positive titre does not therefore exclude the possibility of retinoblastoma.
2. **Ultrasonography** may be useful both in establishing the diagnosis in eyes with hazy media and in excluding other causes of leukocoria. Pseudocystic transformation of the peripheral vitreous appears to be a specific feature of peripheral granulomas.

Choroidal pneumocystosis

Pneumocystis carinii, an opportunistic protozoan parasite, is a major cause of morbidity and mortality in AIDS. Choroidal involvement is an important sign of extrapulmonary dissemination. Most patients with choroiditis have received inhaled aerosolized pentamidine as prophylaxis against *Pneumocystis carinii* pneumonia. This, however, only protects

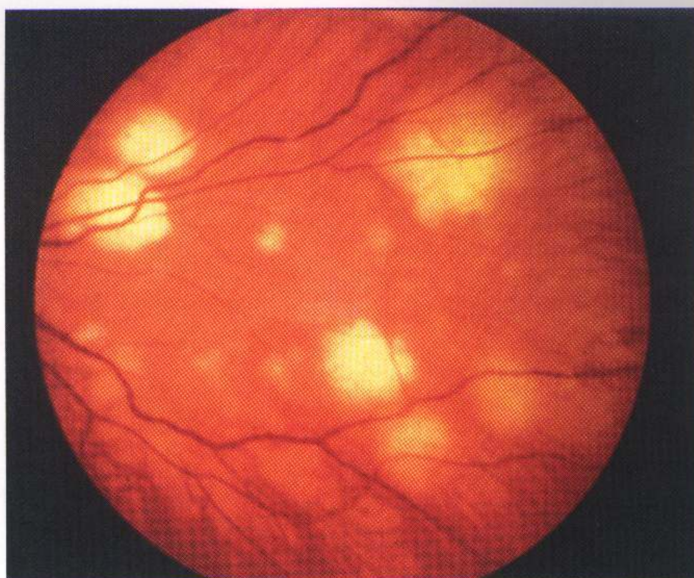


Fig. 10.81
Choroidal pneumocystosis (Courtesy of S. Mitchell)

the lungs and does not prevent the organisms from disseminating throughout the body. Choroiditis implies a grave prognosis for life.

1. **Signs**. Variable number of flat, yellow, round, choroidal lesions which are frequently bilateral (Fig. 10.81). The vitreous is uninvolved and visual acuity usually unimpaired, even in sub-foveal involvement.
2. **Treatment** with intravenous co-trimoxazole (trimethoprim–sulphamethoxazole) or pentamidine effects resolution within several weeks.

Fungal uveitis

Histoplasmosis

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*. Ocular histoplasmosis is asymptomatic unless it causes maculopathy. The vitreous remains clear and is never involved.

Asymptomatic lesions

1. **Atrophic 'histo spots'** are small, roundish, slightly irregular, yellowish-white lesions, scattered throughout the mid-retinal periphery (Fig. 10.82) and posterior pole, which may be associated with small pigment clumps.
2. **Focal peripapillary atrophic** lesions, which are less common, are irregular and punched out, resembling the peripheral spots (Fig. 10.83).
3. **Diffuse parapapillary atrophy** extending up to half a disc diameter beyond the disc margin (Fig. 10.84).
4. **Linear peripheral streaks** of chorioretinal atrophy (Fig. 10.85).

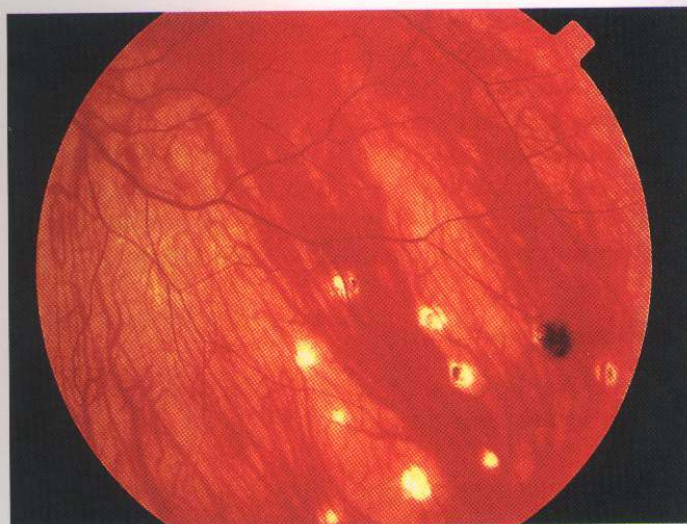


Fig. 10.82
Peripheral 'histo spots'

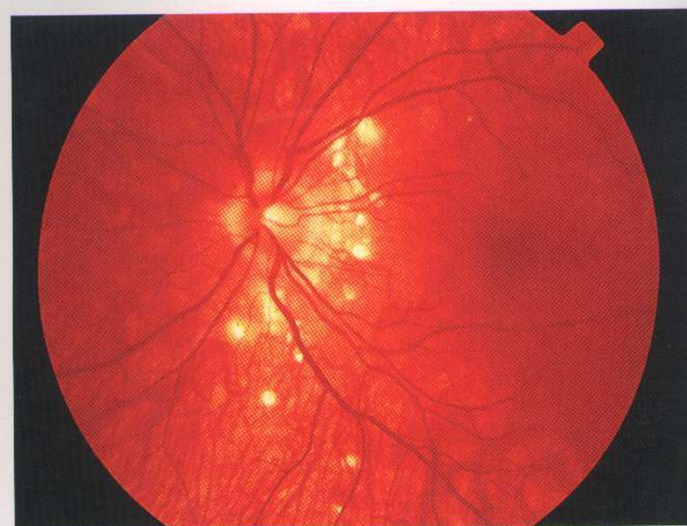


Fig. 10.83
Focal peripapillary atrophic spots in histoplasmosis

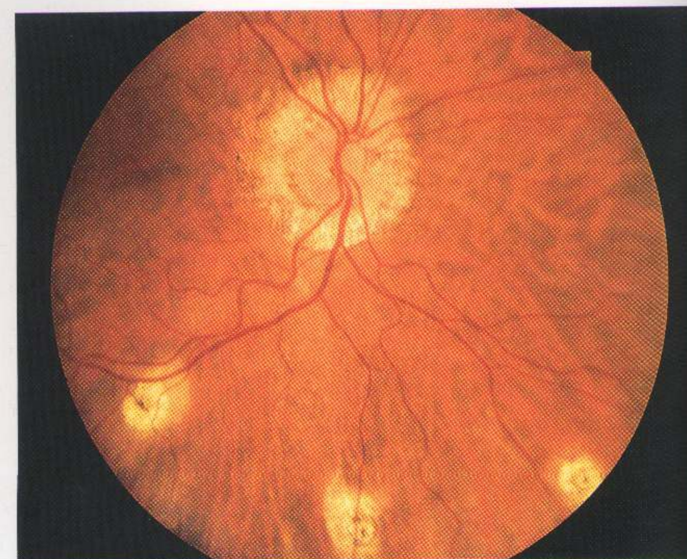


Fig. 10.84
Diffuse parapapillary atrophy and peripheral atrophic spots in histoplasmosis

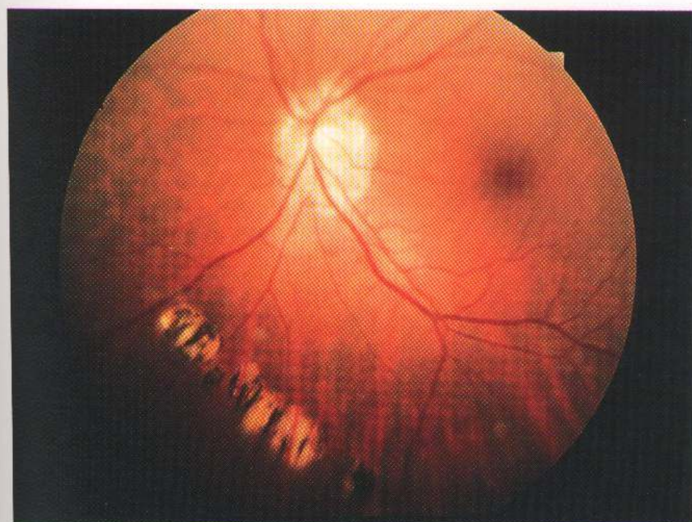


Fig. 10.85
Peripheral linear atrophic streaks in histoplasmosis

Exudative maculopathy

Choroidal neovascularization (CNV) is a late manifestation which usually develops between the ages of 20 and 45 years in about 5% of eyes. In most cases, it is associated with an old macular 'histo spot', although occasionally it may develop within a parapapillary lesion. Very rarely, CNV may occur in the absence of a pre-existing scar.

1. The clinical course of maculopathy is variable.

- The CNV may initially leak fluid and give rise to metamorphopsia, blurring of central vision and a scotoma. Slit-lamp biomicroscopy shows macular elevation by serous fluid and an underlying focal yellow-white or grey lesion. In 12% of eyes the subretinal fluid absorbs spontaneously and visual symptoms regress.
- A dark green-black ring frequently develops on the surface of the yellow-white lesion which bleeds into the subsensory retinal space, causing a marked drop in visual acuity. Rarely the haemorrhage resolves and visual acuity improves.
- In some eyes, the initial CNV remains active for about 2 years, giving rise to repeated haemorrhages. This finally causes profound and permanent impairment of central vision resulting from the development of a fibrous disciform scar at the fovea.

Fig. 10.86
Choroidal neovascularization in histoplasmosis (see text). (**a**) Foveal oedema and haemorrhage; (**b–d**) FA showing juxtafoveal choroidal neovascularization. A 'histo-spot' temporal to the fovea is also present. (Courtesy of S. Milewski)

2. **Monitoring** is important because patients with CNV in one eye and an asymptomatic atrophic macular scar in the other are likely to develop exudative maculopathy in the second eye. They should therefore test themselves daily with an Amsler grid to detect early metamorphopsia because without treatment 60% of eyes with CNV have a final visual acuity of less than 6/60.
3. **Treatment** by laser photocoagulation is currently the treatment of choice of extrafoveal CNV. Pre-treatment fluorescein angiography (FA) is vital in evaluating location and extent of CNV (Fig. 10.86). Surgical removal of subfoveal CNV may be indicated in selected cases. Photodynamic therapy of subfoveal lesions also shows promise.

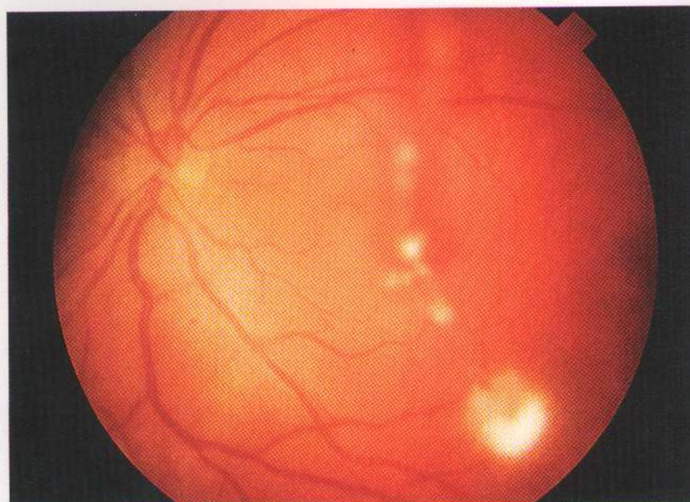


Fig. 10.88
Multifocal candida retinitis

Candidiasis

Candida albicans, a yeast, is a common commensal of the human skin, mouth, gastrointestinal tract and vagina, with a propensity towards opportunistic infection. Candidaemia, which may result in ocular involvement, occurs in three main groups: (a) *intravenous drug addicts*, (b) *patients with long-term indwelling catheters* and (c) *immunocompromised patients*.

Clinical features

1. **Presentation** is with gradual unilateral blurring of vision and floaters.
2. **Signs** (in chronological order)
   - Focal or multifocal choroiditis (Fig. 10.87).
   - Multifocal retinitis manifests as small, round, white, slightly elevated lesions with indistinct borders (Fig. 10.88).
   - Enlargement of the retinal lesions and extension into the vitreous gel, giving rise to floating white 'cotton-ball' colonies (Fig. 10.89).

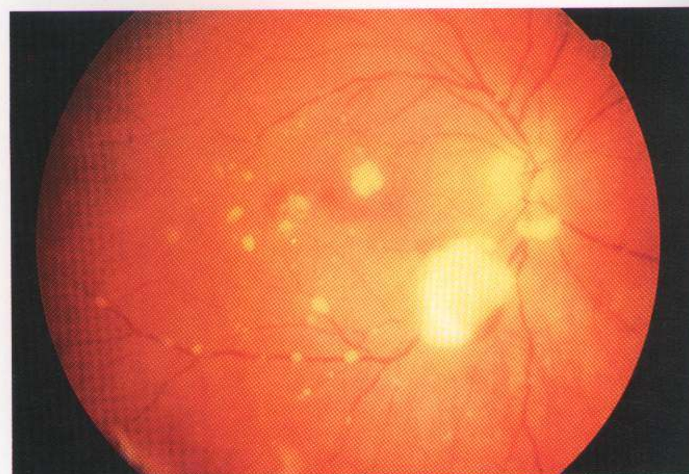


Fig. 10.89
Multifocal candida retinitis with vitreous 'cotton balls' (Courtesy of J. Salmon)



Fig. 10.87
Focal candida choroiditis

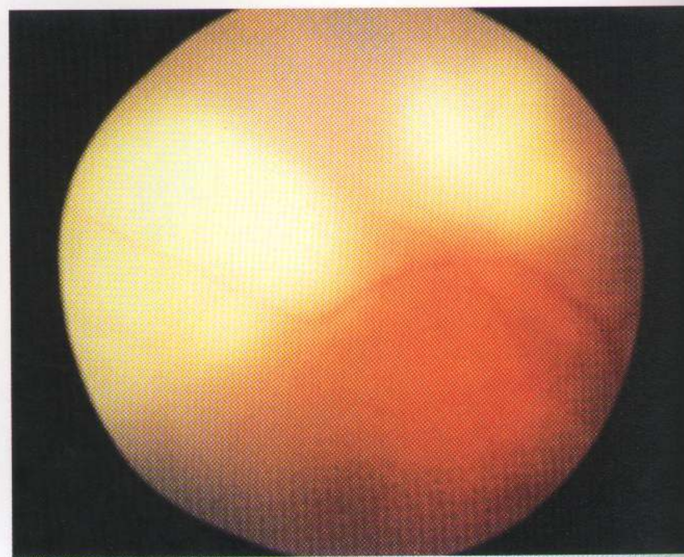


Fig. 10.90
Candida endophthalmitis

- Chronic endophthalmitis characterized by severe vitreous infiltration (Fig. 10.90).
- Retinal necrosis and retinal detachment.

3. **Investigations** involving vitreous cultures and PCR may be required to confirm the diagnosis.

Treatment

1. **Medical treatment** involves a combination of oral 5-fluorocytosine (flucytosine) 150 mg/kg daily and ketoconazole 200–400 mg daily for 3 weeks. Alternative therapy in resistant cases is intravenous amphotericin in 5% dextrose, given over a period of several days until a cumulative dose of 200 mg is reached. The initial daily dose is 5 mg and after a few days this can be increased to 20 mg.
2. **Pars plana vitrectomy** is indicated for endophthalmitis. At vitrectomy, smears and cultures should be taken to confirm the diagnosis and test sensitivity to antifungal agents. Intravitreal injection of 5 μg of amphotericin is also administered.

Cryptococcal choroiditis

Cryptococcus neoformans frequently infects the central nervous system in patients with AIDS, although clinical ocular involvement is rare. When it does occur, it usually follows systemic disease, most commonly cryptococcal meningitis.

1. **Signs** (in chronological order)
   - Multifocal, yellow-white, choroidal lesions which are usually asymptomatic (Fig. 10.91).
   - Retinal involvement characterized by small, glistening spheres at the vitreoretinal interface is rare.
   - Optic nerve involvement may result in rapid visual loss.
2. **Treatment** of sight-threatening lesions is with intravenous amphotericin. Endophthalmitis may require vitrectomy and intravitreal amphotericin.

Mycobacterial uveitis

Tuberculosis

Tuberculosis (TB) is a chronic granulomatous infection caused by bovine (*Mycobacterium bovis*) or human tubercle bacilli (*Mycobacterium tuberculosis*). The former is acquired by drinking milk from infected cattle and the latter by 'droplet infection' (*see* Chapter 20). Tuberculous uveitis is rare in the developed world. However, it may occur without systemic signs of TB, rendering definitive diagnosis difficult. The diagnosis of tuberculous uveitis is therefore often presumptive, based on indirect evidence, such as intractable uveitis unresponsive to steroid therapy and negative findings for other causes of uveitis.

1. **Clinical features**
   a. ***Chronic iridocyclitis***, usually granulomatous, but occasionally non-granulomatous, is the most frequent feature.
   b. ***Choroiditis*** may be focal or multifocal. Rarely, a large solitary choroidal granuloma (Fig. 10.92) may be mistaken for a choroidal tumour.
   c. ***Periphlebitis*** may lead to peripheral retinal capillary closure and neovascularization.
   d. ***Panuveitis***.
2. **Treatment** is with antituberculous drugs.

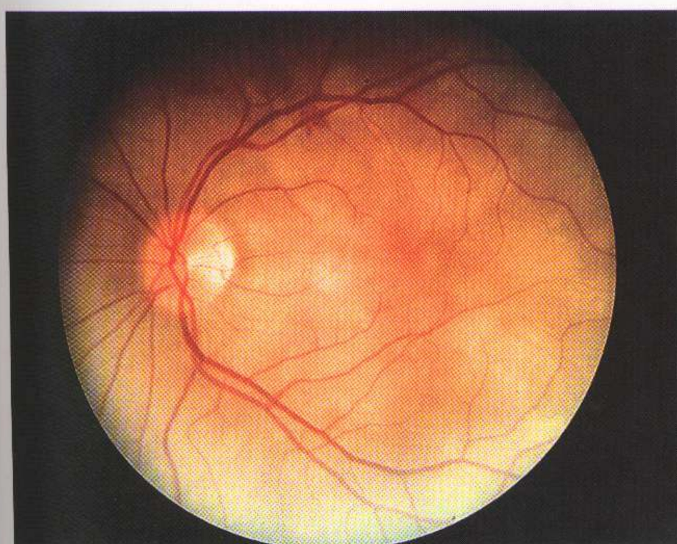


Fig. 10.91
Cryptococcal choroiditis (Courtesy of S. Mitchell)

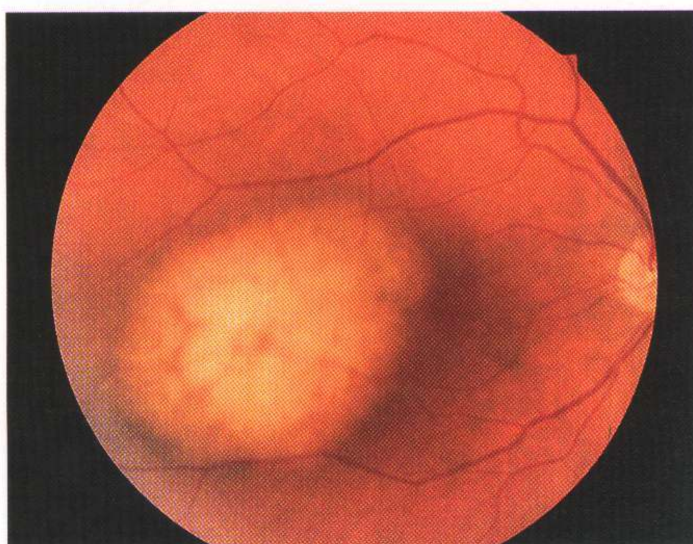


Fig. 10.92
Solitary choroidal tuberculous granuloma

Leprosy

Leprosy (Hansen disease) has the highest incidence of ocular complications of any systemic disease. The pathogenic agent, *Mycobacterium leprae*, has an affinity for skin, peripheral nerves and the anterior segment of the eye. Leprosy may be (a) *lepromatous* or (b) *tuberculoid* (*see* Chapter 20). Uveitis is more common in the former.

1. **Acute iritis** is thought to be caused by immune complex deposition in the uvea. It may be associated with systemic symptoms such as fever and swelling of skin lesions. Intraocular inflammation may be precipitated by initiation or withdrawal of systemic antilepromatous therapy. Treatment is with topical steroids.
2. **Chronic iritis** is the result of direct invasion by bacilli. It is more resistant to conventional therapy than the acute type, because it may not be a true uveitis but a neuro-paralytic inflammation caused by involvement of the iris nerves.
   - A pathognomonic sign of lepromatous leprosy is the presence at the pupillary margin of small, glistening 'iris pearls' resembling a necklace (Fig. 10.93a).
   - The 'pearls' slowly enlarge and coalesce, become pedunculated and drop into the anterior chamber, from which they eventually disappear (Fig. 10.93b).
   - Eventually, the iris becomes atrophic and the pupil miosed (Fig. 10.94).
3. **Other manifestations** include madarosis, trichiasis, conjunctivitis, episcleritis, keratitis and scleritis (Fig. 10.95a). Facial paralysis and anaesthesia, often bilateral, may occur, secondary to involvement of the facial and trigeminal nerves. Keratitis is due to a combination of trichiasis, lagophthalmos (Fig. 10.95b), corneal anaesthesia and secondary infection.

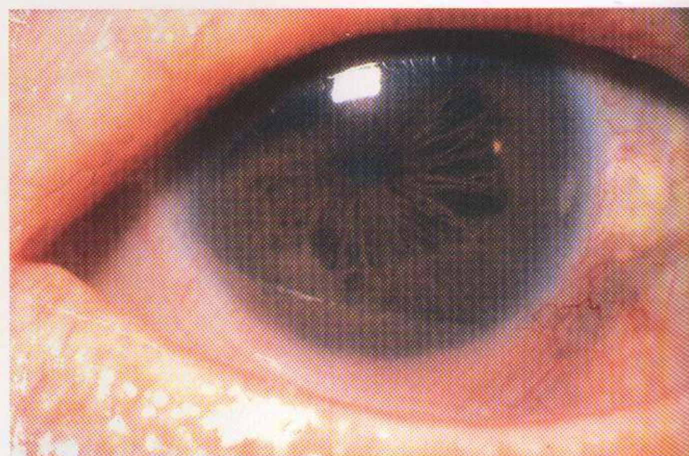


Fig. 10.94
Severe miosis and iris atrophy in chronic lepromatous iritis
(Courtesy of T. ffytche)



Fig. 10.95
Leprosy. (**a**) Severe corneal scarring; (**b**) lagophthalmos
(Courtesy of T. ffytche)

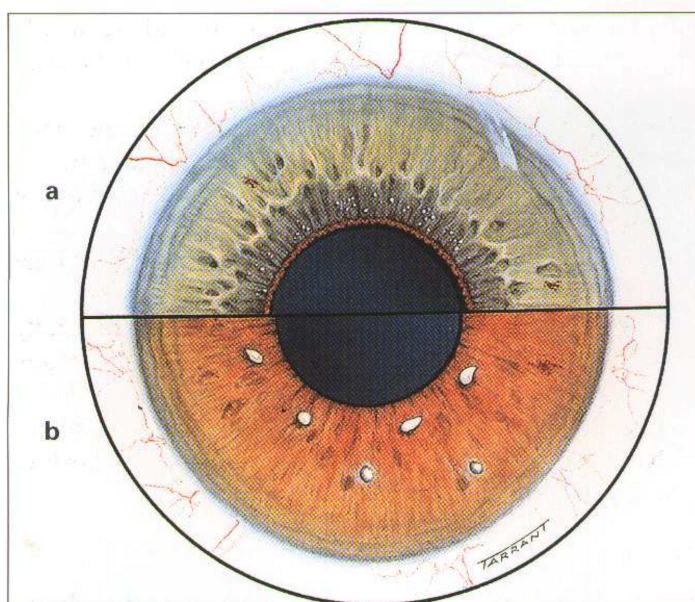


Fig. 10.93
Chronic lepromatous iritis. (**a**) Small iris 'pearls'; (**b**) large iris 'pearls' which have dropped into the anterior chamber

Spirochaetal uveitis

Acquired syphilis

Acquired syphilis is a sexually transmitted infection caused by *Treponema pallidum*. It is a systemic disease which, when untreated, has overt and covert stages (*see* Chapter 20).

Clinical features

Ocular syphilis is uncommon and there are no pathognomonic signs. Eye involvement typically occurs during the secondary and tertiary stages although occasionally it may be seen during primary syphilis. The disease must therefore be suspected in any case of intraocular inflammation resistant to conventional therapy.

1. **External features** include madarosis, scleritis and keratitis.
2. **Iridocyclitis** occurs in about 4% of patients with secondary syphilis and is bilateral in 50%.
   - The inflammation is usually acute and unless appropriately treated becomes chronic.
   - In some cases, iridocyclitis is first associated with dilated iris capillaries (roseolae) (Fig. 10.96), which may develop into more localized papules and subsequently into larger yellowish nodules.
   - Various types of post-inflammatory iris atrophy may ensue.
3. **Multifocal chorioretinitis** is the next most common finding.
   - Multiple foci of choroiditis later evolve into healed lesions, which appear as focal areas of chorioretinal atrophy associated with hyperpigmentation (Fig. 10.97).
   - Occasionally extensive pigmentary changes with perivascular bone spicules, similar to those seen in retinitis pigmentosa, may be associated with night blindness and a ring scotoma.

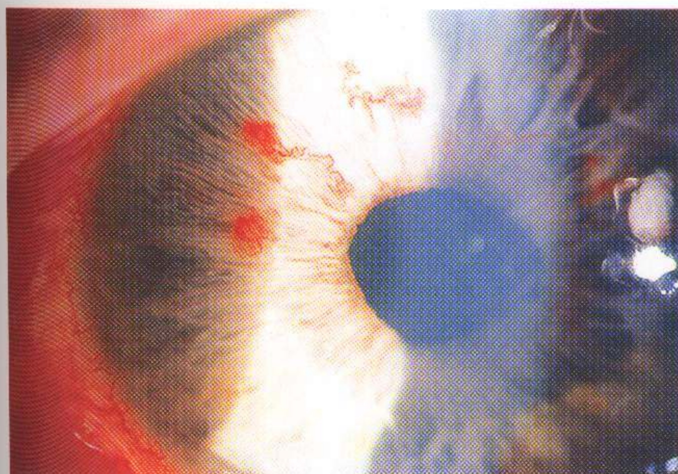


Fig. 10.96
Dilated iris capillaries

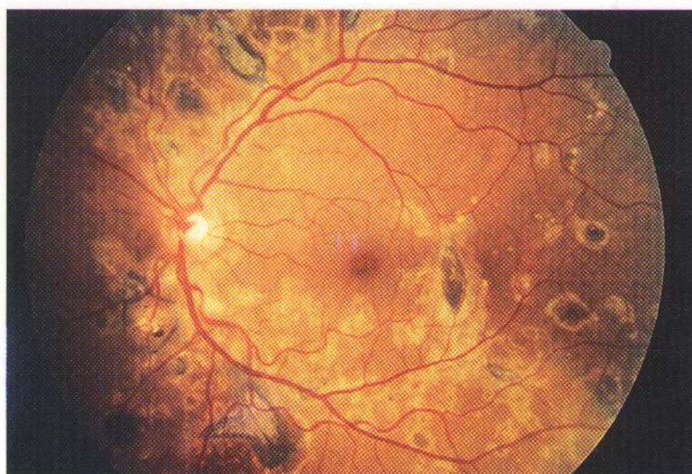


Fig. 10.97
Old multifocal syphilitic choroiditis (Courtesy of J. Salmon)

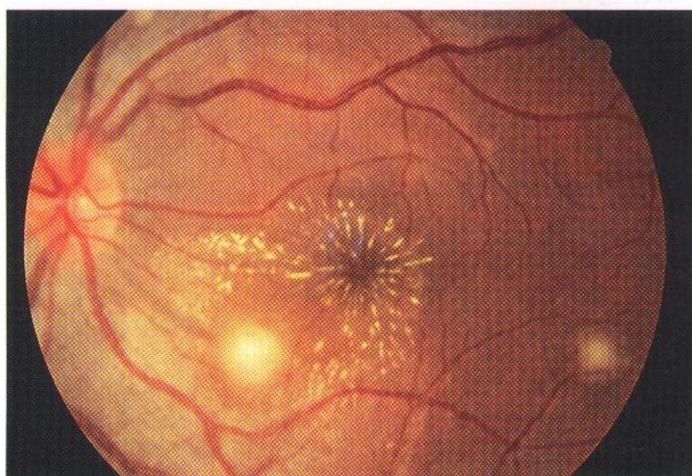


Fig. 10.98
Active syphilitic neuroretinitis (Courtesy of J. Salmon)

4. **Focal chorioretinitis** is less common and frequently bilateral. It is characterized by an inflammatory focus near the disc or at the macula.
5. **Neuroretinitis** primarily involves the retina and optic nerve head independently of choroidal inflammation.
   - The fundus shows disc oedema, engorged veins and a macular star (Fig. 10.98).
   - Cotton wool spots or flame-shaped haemorrhages may appear.
   - Unless treated, the retinal blood vessels eventually become replaced by white strands and optic atrophy ensues (Fig. 10.99).
6. **Neuro-ophthalmological** features include pupillary abnormalities, optic neuropathy, ocular motor nerve palsies and visual field defects.

Treatment

Conventional doses of penicillin are inadequate; the therapeutic regimen is the same as for neurosyphilis (which should be ruled out by lumbar puncture). One of the following regimens may be used:

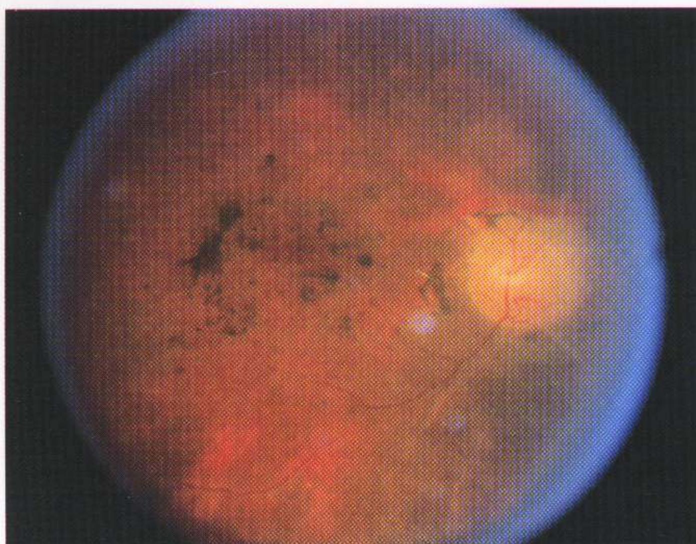


Fig. 10.99
End-stage syphilitic neuroretinitis with vascular attenuation and consecutive optic atrophy

- Intravenous aqueous penicillin G 12–24 mega units (MU) daily for 10–15 days.
- Intramuscular procaine penicillin 2.4 MU daily, supplemented with oral probenecid (2 g daily), for 10–15 days.
- Oral amoxycillin 3 g b.d. for 28 days.
- Penicillin-allergic patients can be treated with oral tetracycline or erythromycin 500 mg q.i.d. for 30 days.

Lyme disease

Lyme disease is caused by *Borrelia burgdorferi*, which is similar to the treponeme that causes syphilis. It is transmitted through the bite of its vector, the deer tick *Ixodes* sp. As with syphilis, both early and late manifestations develop in many organ systems (*see* Chapter 20).

1. **Uveitis** may take the form of granulomatous iridocyclitis, intermediate uveitis, retinal vasculitis and occasionally peripheral multifocal choroiditis.
2. **Neuro-ophthalmological features** include optic neuritis, neuroretinitis and ocular motor nerve palsies.
3. **Other features** include periorbital oedema, conjunctivitis, episcleritis, keratitis and orbital myositis.
4. **Treatment** is with doxycycline 100 mg b.d. for 2–3 weeks.

Common specific uveitis entities

Fuchs uveitis syndrome

Fuchs uveitis syndrome (FUS) or Fuchs heterochromic cyclitis is a chronic, non-granulomatous, anterior uveitis of insidious onset. It typically affects one eye of a young adult, although it can also occur during childhood and may rarely be bilateral. Although FUS accounts for about 4% of all cases of uveitis, it is frequently misdiagnosed and overtreated. The heterochromia (difference in iris colour) may be absent or difficult to detect, particularly in brown-eyed individuals, unless the patient is examined in daylight with undilated pupils.



Fig. 10.100
Heterochromia iridis and cataract in left Fuchs uveitis syndrome

Presentation

- Gradual blurring of vision secondary to cataract formation is the most common.
- Chronic annoying floaters.
- Colour difference between the two eyes (Fig. 10.100).
- Incidental detection.

General signs

1. **Keratic precipitates** (KP) are characteristic and possibly pathognomonic. They are small, round or stellate, grey-white in colour and scattered throughout the corneal endothelium (Fig. 10.101). They may come and go but never become confluent or pigmented. Feathery fibrin filaments may be seen in between the KP.

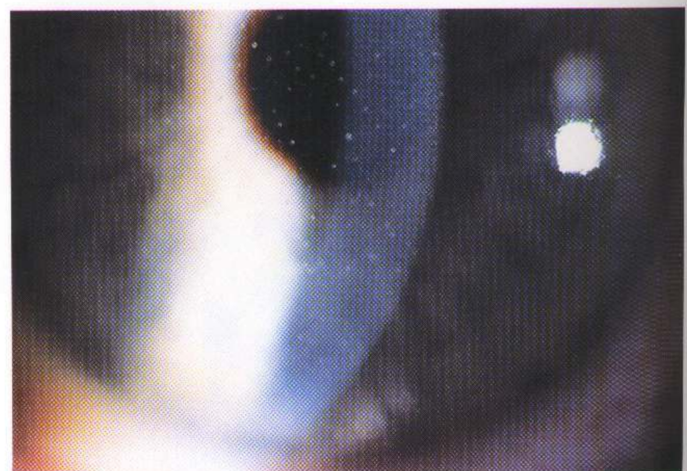


Fig. 10.101
Keratic precipitates in Fuchs uveitis syndrome

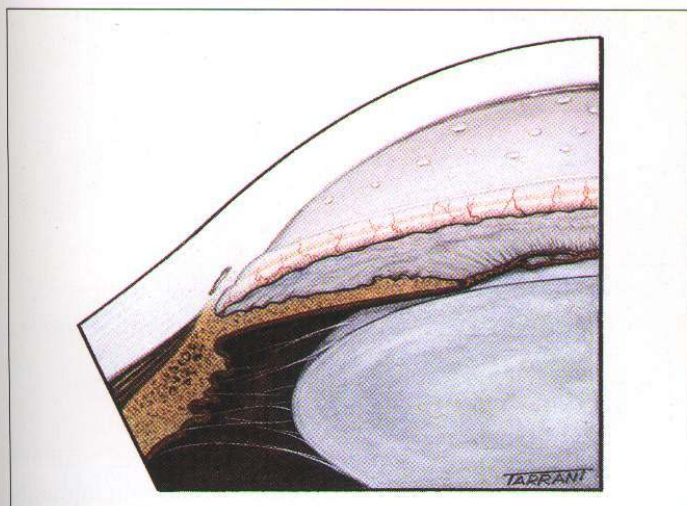
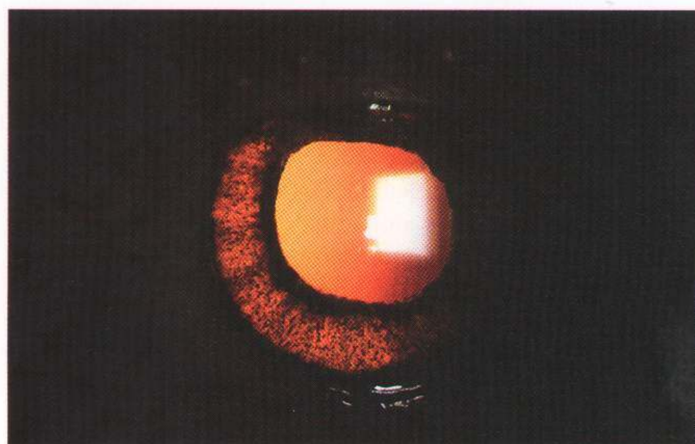


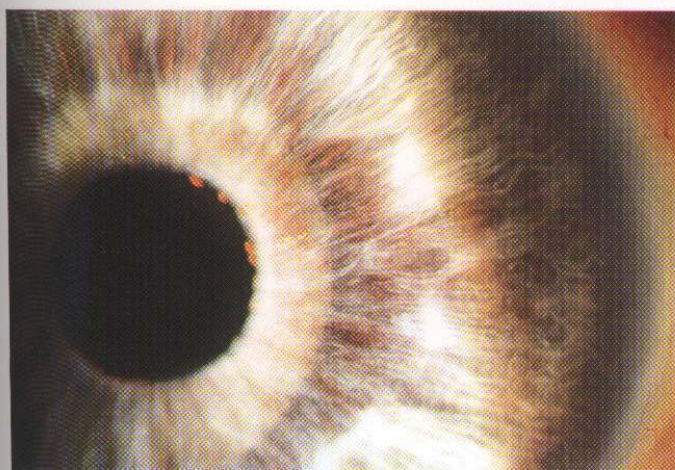
Fig. 10.102
New vessels in the angle in Fuchs uveitis syndrome

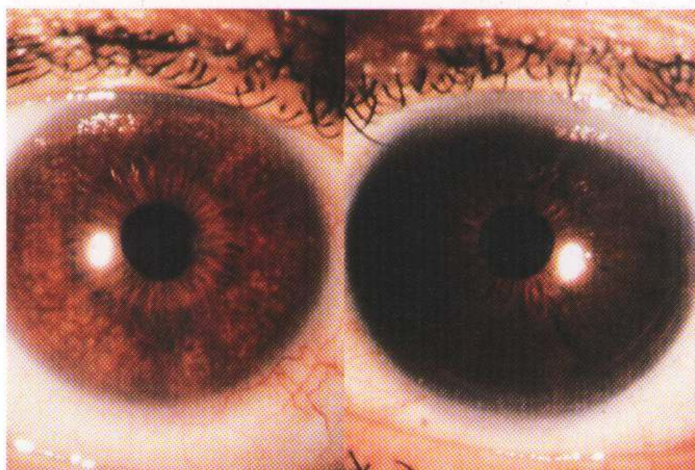

Fig. 10.104
Transillumination defects due to iris atrophy in Fuchs uveitis syndrome

2. **Aqueous humour** shows a faint flare and never more than +2 cells.
3. **Vitritis** and stringy opacities are common and may be the presenting symptom.
4. **Gonioscopy** may be normal or may show one of the following:
   - Fine radial twig-like vessels in the angle (Fig. 10.102) are common and are probably responsible for the filiform haemorrhages which develop on anterior chamber paracentesis opposite the puncture site (Amsler sign).
   - A membrane obscuring angle details.
   - Small, non-confluent, irregular, peripheral anterior synechiae.

Iris signs

1. **Posterior synechiae do not occur**, except after cataract surgery.
2. **Diffuse stromal iris atrophy**
   - The earliest finding is loss of iris crypts.
   - Advanced stromal atrophy makes the affected iris appear dull with loss of detail, giving rise to a washed-out appearance, particularly in the pupillary zone (Fig. 10.103).
   - The normal radial iris blood vessels appear prominent due to lack of stromal support.
3. **Posterior pigment layer iris atrophy** is patchy and best detected by retroillumination (Fig. 10.104).
4. **Iris nodules** may be present.
5. **Rubeosis iridis** consisting of fine, irregular, fragile, neovascularization on the iris surface is fairly common.
6. **Mydriasis** resulting from atrophy of the pupillary sphincter may be present.
7. **Iris crystals** occur in a minority of cases.
8. **Heterochromia iridis** is an important and common sign.
   - Most frequently the affected eye is hypochromic (Fig. 10.105) although in about 10% it is hyperchromic.
   - In a small proportion of cases, the heterochromia is congenital.
   - The nature of heterochromia is determined by the relative degrees of atrophy of the stroma and posterior pigment epithelium, as well as the patient's natural iris colour.


Fig. 10.103
Stromal iris atrophy in Fuchs uveitis syndrome


Fig. 10.105
Heterochromia iridis in right Fuchs uveitis syndrome

- Predominantly stromal atrophy allows the posterior pigmented layer to show through and become the dominant pigmentation, so that the eye becomes hyperchromic.
- In general, a brown iris becomes less brown and a blue iris assumes a more saturated blue colour.

Complications

FUS runs a chronic course lasting many years. The two main complications are cataract and glaucoma, both of which may be enhanced by the inadvertent use of topical steroids.

1. **Cataract** is extremely common and does not differ from that associated with other types of anterior uveitis. The results of surgery with posterior chamber intraocular lens implantation are good, although the operation may be complicated by hyphaema.
2. **Glaucoma** is the most serious threat to vision and is frequent when the follow-up period is long (*see* Chapter 9).

Treatment

1. **Topical steroids** are ineffective.
2. **Mydriatics** are unnecessary because posterior synechiae do not occur.
3. **Posterior sub-Tenon** injections of a long-acting preparation such as triamcinolone acetonide may be beneficial for troublesome vitreous floaters although improvement is usually temporary.
4. **Vitrectomy** may be considered for severe vitreous opacification, unresponsive to periocular steroid injections.

Differential diagnosis of heterochromia iridis

Apart from FUS, the following conditions may give rise to heterochromia:

1. **Hypochromia**
   - Congenital.
   - Horner syndrome, particularly if congenital.
2. **Hyperchromia**
   - Oculodermal melanocytosis (naevus of Ota).
   - Ocular siderosis.
   - Diffuse iris naevus or melanoma.
   - Unilateral use of topical latanoprost.
   - Sturge–Weber syndrome (rare).

Intermediate uveitis

Intermediate uveitis is an idiopathic, insidious, inflammatory disease affecting the pars plana, peripheral retina and underlying choroid. It accounts for about 8% of all cases of uveitis. Although often bilateral, involvement is frequently asymmetrical. On long-term follow-up 10–15% of patients subsequently develop multiple sclerosis, a common immunogenetic predisposition appearing to be HLA-DR15.

Clinical features

1. **Presentation** is in the second to fourth decades with increasing floaters, or less commonly with impairment of central vision secondary to macular oedema.
2. **Signs**
   a. ***Vitritis*** is predominant although the anterior chambers may display mild activity. The severity of vitritis may vary.
      - Cells in the anterior vitreous (Fig. 10.106).
      - Gelatinous exudates ('snowballs' or 'cotton balls') (Fig. 10.107).
      - Sheet-like condensations in long-standing cases (Fig. 10.108).
      - Rarely the entire vitreous may become opaque (Fig. 10.109).

   b. ***Peripheral retinal periphlebitis*** is common and usually mild.

   c. ***Snowbanking*** is the hallmark of pars planitis, which is a subset of intermediate uveitis. It consists of a grey-white plaque involving the inferior pars plana, visible



Fig. 10.106
Anterior vitreous cells in intermediate uveitis

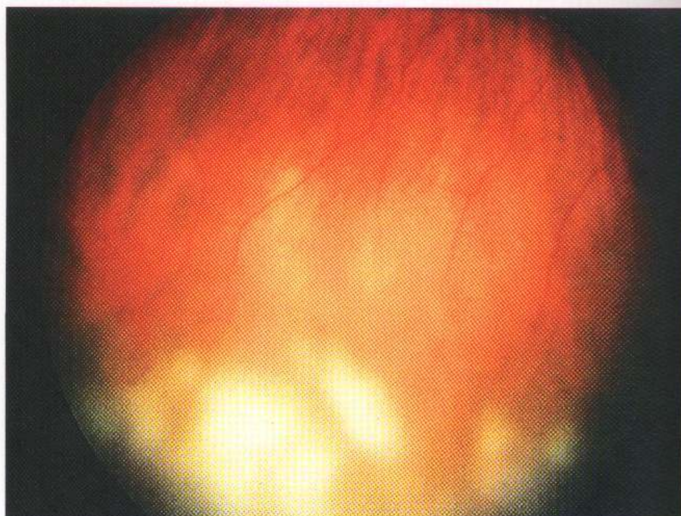
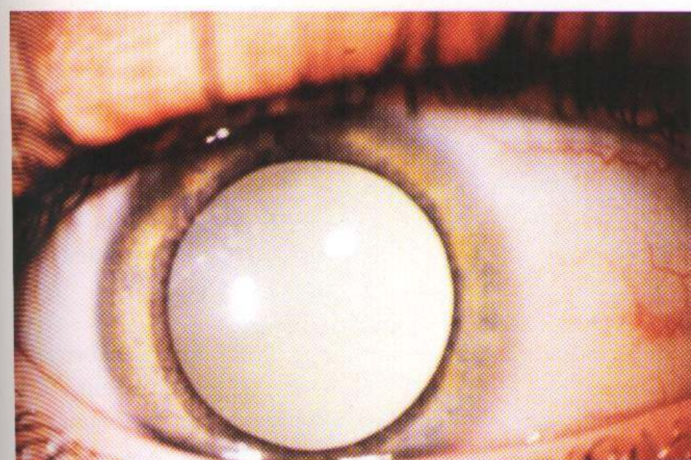
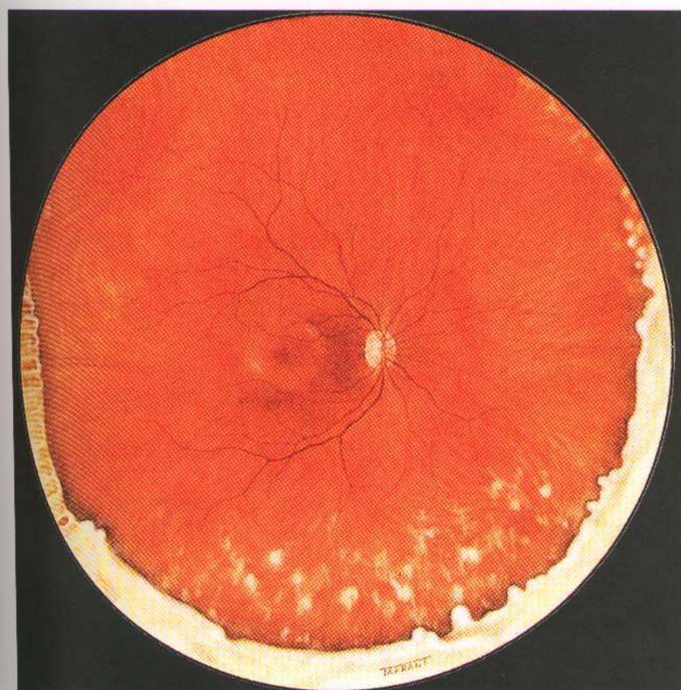


Fig. 10.107
Vitreous 'cotton balls' in intermediate uveitis


Fig. 10.108
Vitreous condensations in long-standing intermediate uveitis


Fig. 10.109
Severe vitreous opacification in intermediate uveitis


Fig. 10.110
Inferior 'snowbanking' in pars planitis

only on indirect ophthalmoscopy with scleral indentation (Fig. 10.110). In advanced cases the plaque may extend posteriorly to cover the peripheral retina.

3. **Course**. Some patients have a single, mild, self-limiting episode lasting a few months but most have chronic smouldering inflammation lasting several years, with multiple subacute exacerbations and incomplete remissions. Despite this, the prognosis is relatively good.

Complications

1. **Cystoid macular oedema** is the most common cause of visual impairment.
2. **Macular epiretinal gliosis** is also frequent.
3. **Secondary cataract** develops more frequently in eyes with severe and prolonged inflammation.
4. **Tractional retinal detachment** may occur in advanced cases as a result of contraction of fibrovascular tissue at the pars plana (which may also result in vitreous haemorrhage).
5. **Cyclitic membrane formation** is the result of massive proliferation of vascularized exudate on to and behind the posterior lens capsule. Traction by the membrane on the ciliary body may cause ciliary detachment, with diminished secretion of aqueous, resulting in ocular hypotony and eventual phthisis bulbi.

Treatment

It is important not to over-treat this condition. The main indication for treatment is a visual acuity of 6/12 or less secondary to persistent cystoid macular oedema.

1. **Posterior sub-Tenon injections** of triamcinolone acetonide (Kenalog) or methylprednisolone acetate (Depomedrone) are effective in most cases. The necessity for repeated injections is governed by visual acuity rather than severity of vitritis.
2. **Systemic** steroids or immunosuppressive agents may be required if resistant to periocular steroids.
3. **Cryotherapy** to the vitreous base may be beneficial in controlling inflammation and active neovascularization.
4. **Pars plana vitrectomy** may be required for severe and persistent complications such as vitreous haemorrhage, dense vitreous opacification, epiretinal membranes and tractional retinal detachment.

Differential diagnosis

The following conditions may also be characterized by vitreous inflammation in the absence of significant retinal findings:

1. **Fuchs uveitis syndrome**
   - Similarities: may affect young individuals and present with floaters and mild anterior uveitis.
   - Differences: unilateral and subtle iris atrophy is present in the majority of cases.
2. **Systemic diseases** which may be associated with 'secondary intermediate uveitis' include sarcoidosis, Lyme

disease, non-Hodgkin B-cell lymphoma, cat-scratch fever and Whipple disease.

Juvenile chronic iridocyclitis

While juvenile idiopathic arthritis is the most common systemic association of chronic iridocyclitis in children, many patients with juvenile chronic iridocyclitis are otherwise healthy. The majority of patients are also girls. As the onset of intraocular inflammation is frequently insidious and asymptomatic, most cases are not diagnosed until visual acuity is reduced from complicated cataract or the parents notice a white patch on the cornea caused by band keratopathy (Fig. 10.111). In a small number of cases the uveitis is detected by chance.

Acute anterior uveitis in young adults

While ankylosing spondylitis is the most common systemic association of acute anterior uveitis (Fig. 10.112), many patients have no underlying systemic disease, although about 45% carry HLA-B27. The risk to HLA-B27 negative patients (particularly females) of subsequently developing ankylosing spondylitis is very small, although some HLA-B27 positive patients (particularly males) will subsequently develop the disease.



Fig. 10.111
Band keratopathy in juvenile chronic iridocyclitis

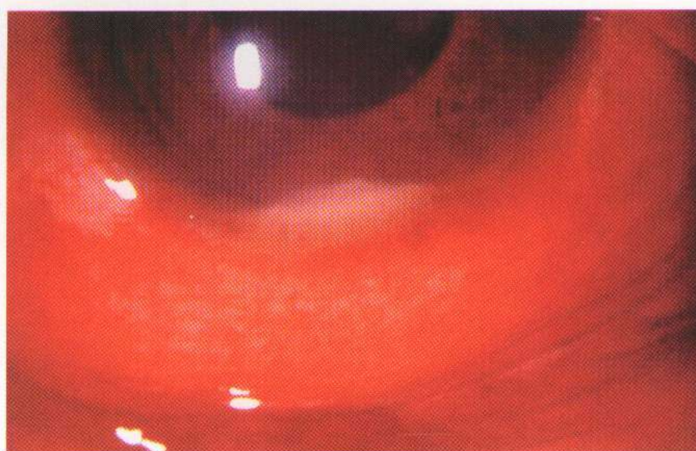


Fig. 10.112
Acute anterior uveitis with hypopyon in ankylosing spondylitis

Idiopathic multifocal white dot syndromes

Acute multifocal posterior placoid pigment epitheliopathy

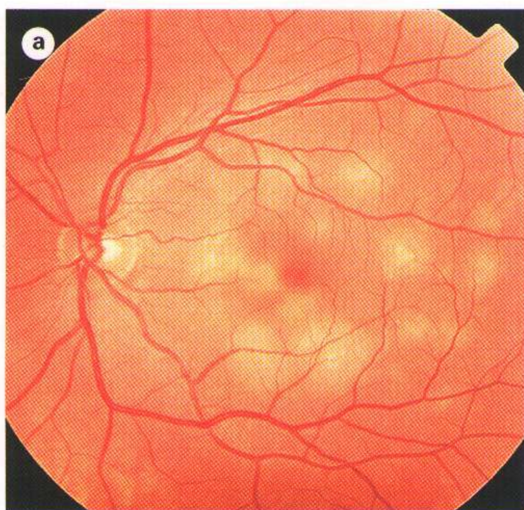
Acute multifocal posterior placoid pigment epitheliopathy (AMPPPE) is an uncommon, idiopathic, bilateral, self-limiting condition which is frequently associated with HLA-B7 and HLA-DR2. Although there is no treatment the prognosis is good.

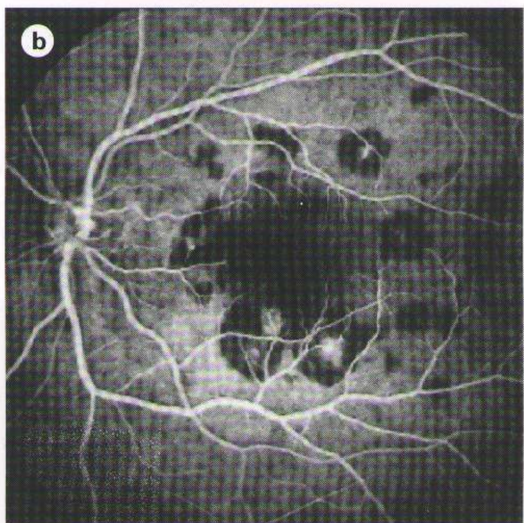
1. **Presentation** is in the third to fifth decades with subacute unilateral visual impairment which becomes bilateral within a few days. About a third of patients have a preceding 'flu-like' illness which may be associated with erythema nodosum.
2. **Signs**
   - Multiple, large, cream or greyish-white, subretinal, plaque-like lesions of variable size which begin at the posterior pole and then extend to the post-equatorial fundus (Fig. 10.113a).
   - Associated findings include anterior uveitis, mild vitritis, disc oedema and retinal periphlebitis.
3. **FA** of active lesions shows early dense hypofluorescence due to blockage of choroidal fluorescence (Fig. 10.113b). The late phase shows hyperfluorescence due to staining (Fig. 10.113c). These findings can be explained on the basis of occlusion of the choriocapillaris which leads to swelling of the retinal pigment epithelium (RPE).
4. **Course**. After a few weeks the fundus lesions gradually subside and within a few months visual acuity returns to normal or near normal. Variable residual signs consist of multifocal areas of RPE depigmentation and clumping (Fig. 10.114). Some patients complain of residual paracentral visual field defects and a few develop late CNV.

Serpiginous choroidopathy

Serpiginous choroidopathy is an uncommon, idiopathic, bilateral, progressive disease.

1. **Presentation** is in the fourth to sixth decades with unilateral blurring of vision or metamorphopsia. After a variable period of time the fellow eye is also affected although it is not uncommon to find evidence of inactive asymptomatic disease in the fellow eye at the time of presentation.





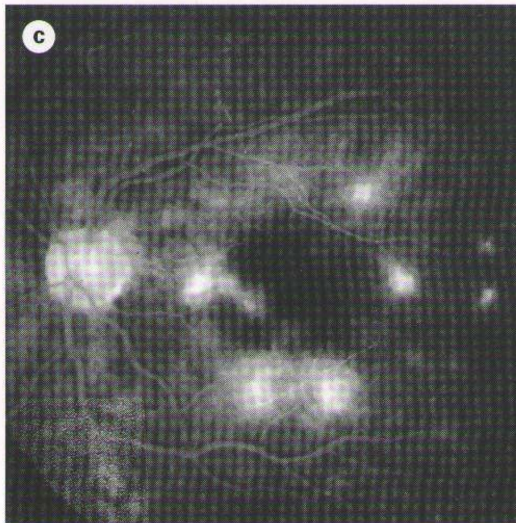


Fig. 10.113
Acute multifocal posterior placoid pigment epitheliopathy (*see text*) (Courtesy of S. Milewski)

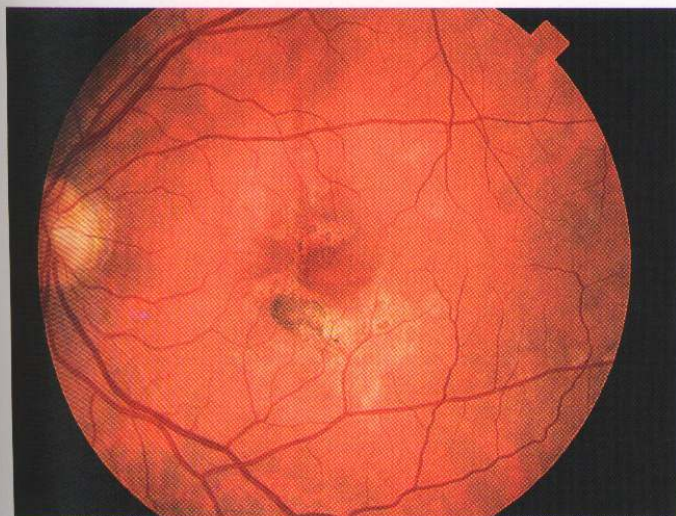


Fig. 10.114
Resolved acute multifocal posterior placoid pigment epitheliopathy

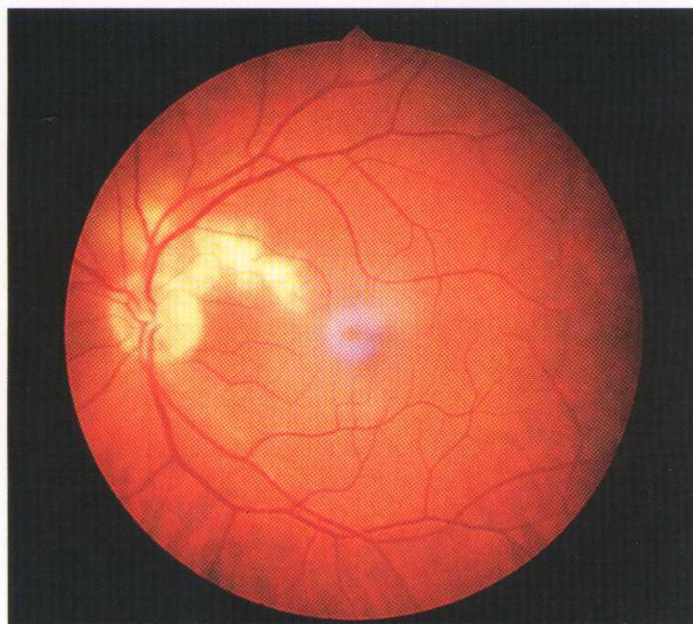


Fig. 10.115
Early serpiginous choroidopathy

2. Signs

- Active lesions are grey-white to yellow-white subretinal infiltrates with hazy borders, which later become brighter. They typically start around the optic disc (Fig. 10.115) and then gradually spread outwards in a snake-like manner and towards the macula (Fig. 10.116).

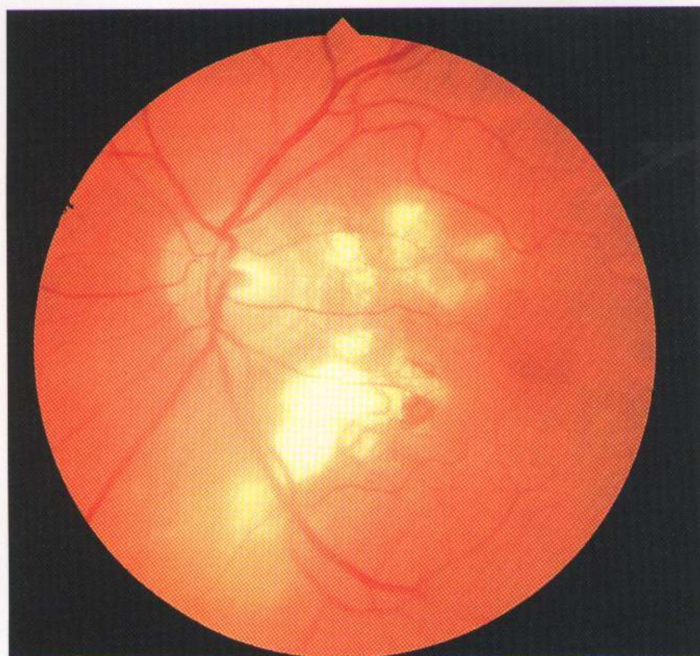


Fig. 10.116
More advanced serpiginous choroidopathy

Rarely the initial lesion involves the macula.
- Associated features include vitritis and mild anterior uveitis.

3. **FA** shows early hypofluorescence due to blockage and late hyperfluorescence due to staining.
4. **Electro-oculogram (EOG)** is subnormal.
5. **Course** is prolonged, lasting many years, in an episodic and recurrent fashion. Disease activity not uncommonly recurs after several months of remission. Recurrences are characterized by yellow-grey extensions of choroiditis (at the level of the choriocapillaris), contiguous with or as satellites to pre-existing areas of chorioretinal atrophy. Inactive lesions are characterized by scalloped, atrophic, 'punched-out' areas of choroidal atrophy associated with RPE changes. The long-term visual prognosis is poor, with permanent visual loss caused by foveal involvement occurring in about 50% of cases (Fig. 10.117). Some eyes develop CNV associated with an old scar which may be amenable to laser photocoagulation. Subretinal fibrosis is a rare late complication.

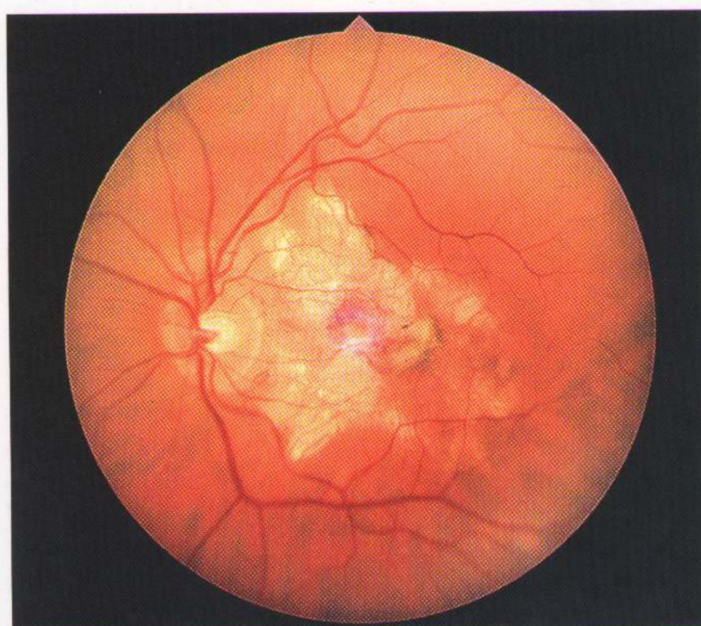


Fig. 10.117
Extensive involvement of the posterior pole in serpiginous choroidopathy

6. **Treatment** options include triple therapy with systemic steroids, azathioprine and cyclosporin although early monotherapy with cyclosporin may be adequate.

Birdshot retinochoroidopathy

Birdshot retinochoroidopathy is an uncommon, chronic, bilateral inflammatory disease, probably of autoimmune aetiology. About 90% of patients are positive for HLA-A29.

1. **Presentation** is in the sixth to seventh decades with blurring of vision, frequently associated with nyctalopia, disturbance of colour vision and floaters. The severity of visual disturbance is frequently out of proportion to the visual acuity, indicating diffuse retinal dysfunction.

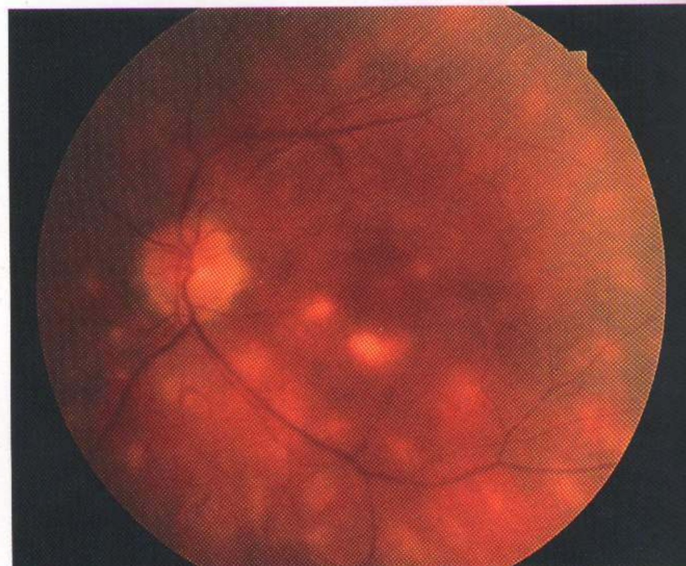


Fig. 10.118
Birdshot retinochoroidopathy involving the macula and mid-periphery

2. **Signs**
   - Diffuse vitritis but minimal if any anterior uveitis.
   - Acute lesions consist of distinctive, subretinal, poorly defined, cream-coloured, small (100–300 μm) ovoid spots distributed in one of four patterns:
     a. Involving the macula and mid-periphery (Fig. 10.118, *see* Fig. 10.121a).
     b. With relative macular sparing (Fig. 10.119).
     c. With macular predominance.

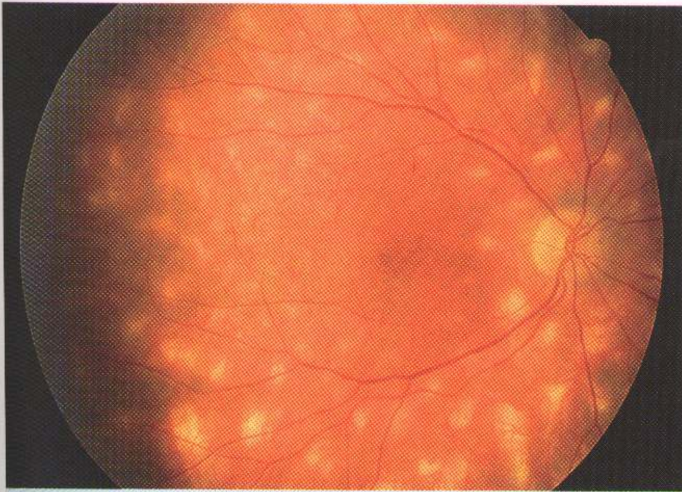


Fig. 10.119
Birdshot retinochoroidopathy with macular sparing

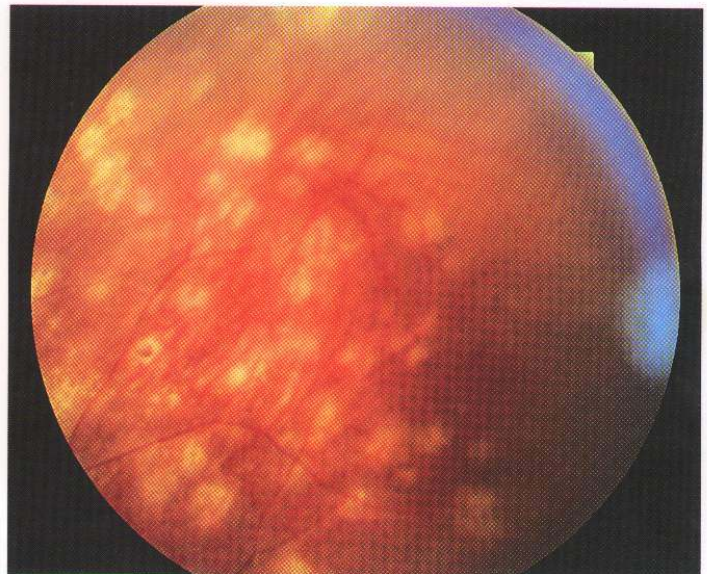
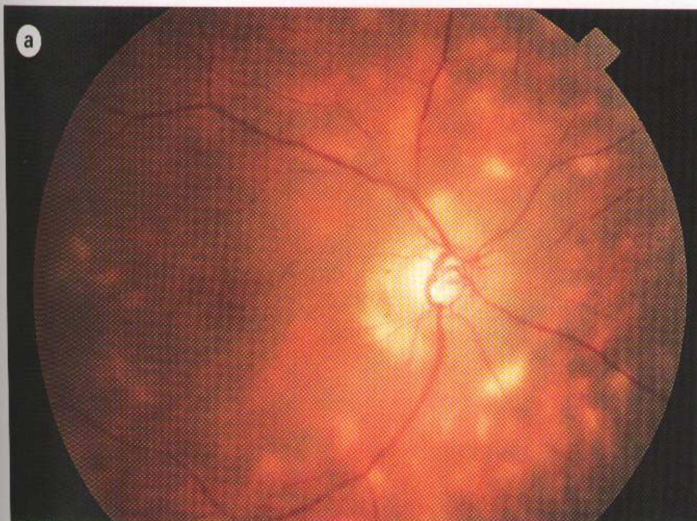


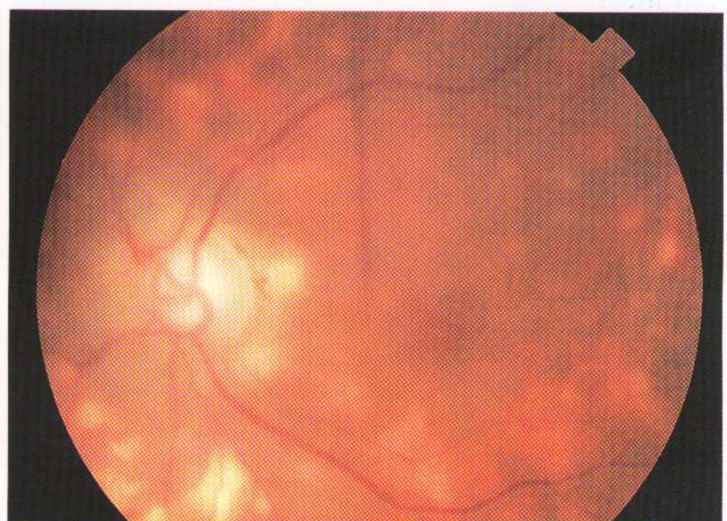
Fig. 10.120
Resolved birdshot retinochoroidopathy

d. Asymmetrical with inferonasal predominance of lesions and relative macular sparing.

- Over time the lesions may become confluent. Inactive lesions consist of well-delineated, white atrophic spots (Fig. 10.120).

3. **FA** of established active lesions shows disc staining and vascular leakage (Fig. 10.121b) but early birdshot lesions





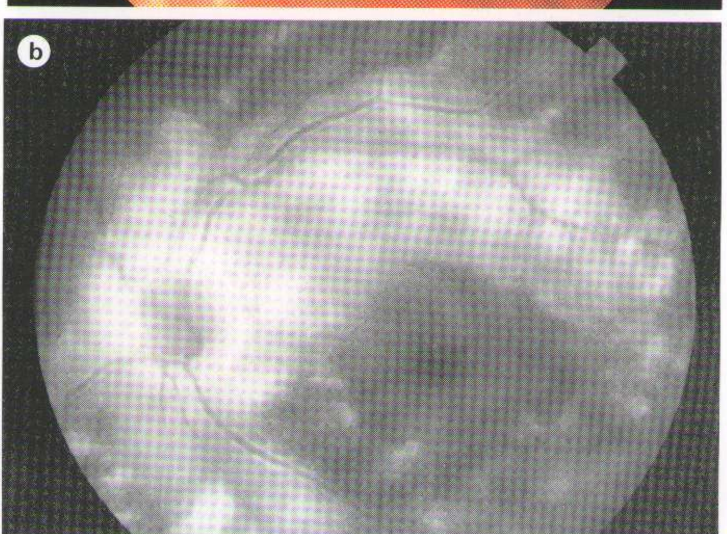


Fig. 10.121
Birdshot retinochoroidopathy (*see text*) (Courtesy of S. Milewski)

may remain silent throughout the angiogram, so that a greater number are seen clinically than angiographically.

4. **ICG** detects birdshot lesions more readily than FA. Typical findings in active disease are hypofluorescent dark spots during the intermediate phase of the angiogram which remain so, or become isofluorescent during the late phases. Two other features are indistinct choroidal vessels and late diffuse choroidal hyperfluorescence.
5. **Electroretinogram (ERG)** is subnormal.
6. **Course**. About 20% of patients have a self-limited course and maintain normal visual acuity. The remainder have a chronic course with exacerbations and remissions over several years with visual impairment due to CMO and occasionally epiretinal gliosis and CNV.
7. **Treatment**. Although currently there is no definitive treatment strategy the following may be considered:
   a. ***Steroids***, both periocular or systemic, give inconsistent results.
   b. ***Cyclosporin***, in uncontrolled studies, has been shown to be superior to steroid therapy and may prove to be the treatment of choice.

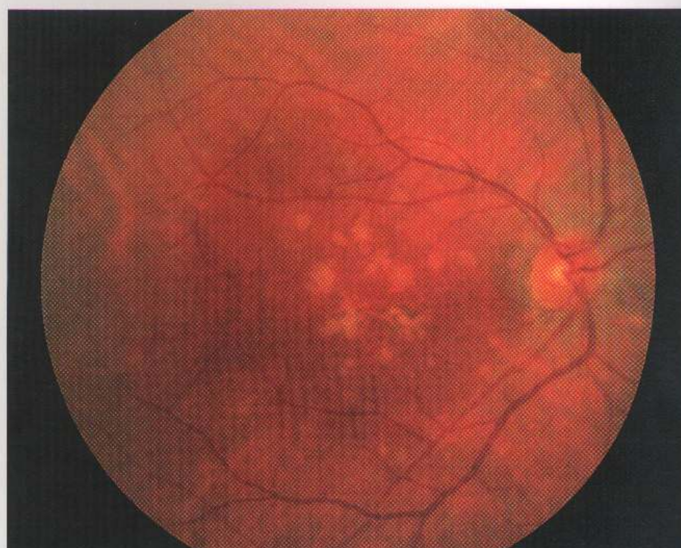


Fig. 10.123
Inactive punctate inner choriodopathy

Punctate inner choroidopathy

Punctate inner choroidopathy (PIC) is an uncommon, idiopathic, bilateral disease which typically affects myopic women.

1. **Presentation** is in the fourth to fifth decades with blurring of central vision, frequently associated with photopsia. In some cases photopsia may be present for several weeks prior to the development of clinical signs.
2. **Signs** (in chronological order)
   - Multiple, small, deep, yellow, indistinct spots involving the posterior pole, all at the same stage of evolution (Fig. 10.122). Plentiful lesions may be associated with serous sensory retinal elevation.
   - After a few weeks the acute lesions resolve, leaving behind sharply demarcated atrophic scars which may later enlarge and become pigmented (Fig. 10.123).
   - There is no intraocular inflammation.

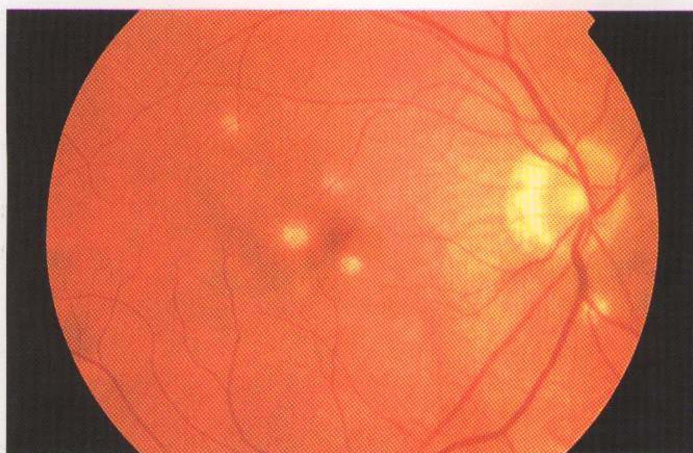


Fig. 10.122
Active punctate inner choroidopathy (Courtesy of Moorfields Eye Hospital)

3. **FA** shows hyperfluorescence of the lesions due to RPE window defects and, if present, CNV (Fig. 10.124b–d).
4. **ERG** is normal.
5. **Course**. After a variable period of time the fellow eye frequently becomes involved. Some patients develop foveal scarring or secondary CNV associated with a scar within a year of presentation. The prognosis is relatively good in patients without macular involvement.
6. **Treatment** is only possible for CNV with the following modalities:
   a. ***Laser photocoagulation***.
   b. ***Systemic steroids*** may reduce subretinal vascular leakage and stabilize vision.
   c. ***Surgical excision*** of subfoveal CNV may be appropriate in selected cases.

Multifocal choroiditis with panuveitis

Multifocal choroiditis with panuveitis is an uncommon, usually bilateral, recurrent inflammatory disease. Although the aetiology is obscure, Epstein–Barr virus infection may be responsible. Females are more commonly affected, in a 3:1 ratio.

Clinical features and treatment

1. **Presentation** is in the fourth decade with blurring of vision, which may be associated with floaters and photopsia.
2. **Signs**
   - Vitritis is universal; anterior uveitis is present in 50% of cases.
   - Multiple, discrete, small, round or ovoid, deep, yellowish-grey lesions located at the posterior pole and periphery (Fig. 10.125).
   - Other features include blind spot enlargement and occasionally mild disc oedema.

Fig. 10.124
Choroidal neovascularization in punctate inner choroidopathy (*see text*) (Courtesy of S. Milewski)

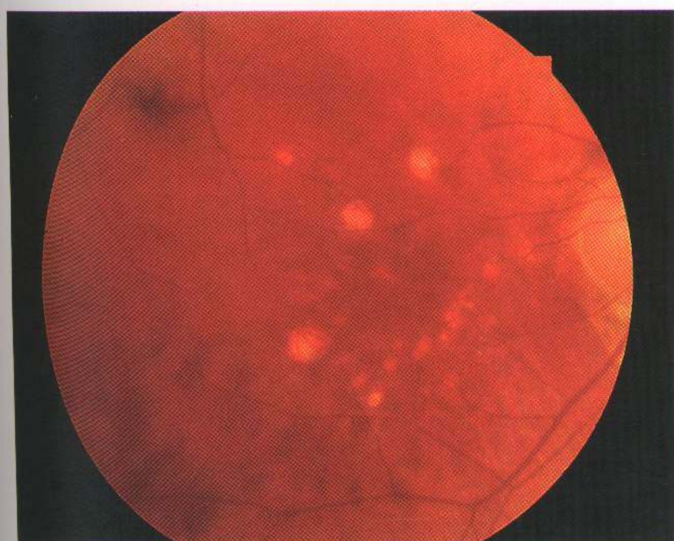


Fig. 10.125
Active multifocal choroiditis with panuveitis

3. **FA** of active lesions shows early blockage and late staining. Old inactive lesions show early hyperfluorescence which subsequently fades during the late phase.
4. **ERG** is normal or mildly subnormal.
5. **Course** may last many months with the development of fresh lesions and recurrent inflammatory episodes. Inactive lesions have sharp 'punched-out' margins and pigmented borders (Fig. 10.126). The prognosis is guarded because central vision may be impaired by direct foveal involvement, secondary CNV associated with a scar, CMO and occasionally diffuse subretinal fibrosis (Fig. 10.127).
6. **Treatment** with systemic steroids is effective in at least 50% of cases, although immunosuppressive agents are often necessary to reduce the complications of long-term systemic steroid therapy. Eyes with CNV may require laser photocoagulation.

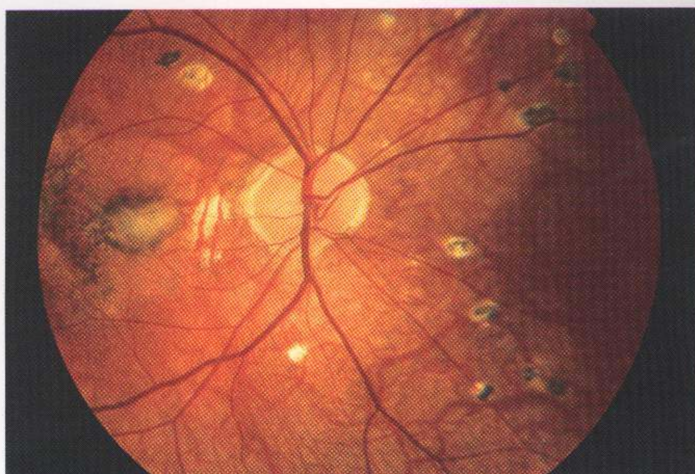
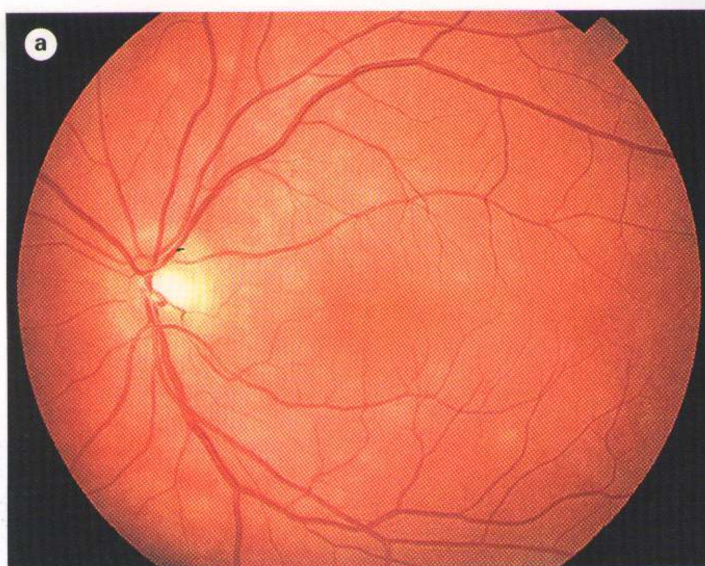


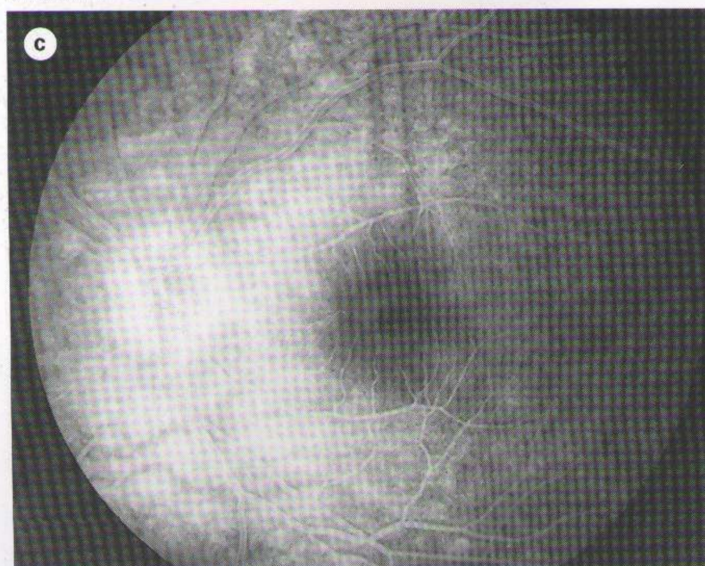
Fig. 10.126
Inactive multifocal choroiditis with panuveitis



Fig. 10.127
Diffuse subretinal fibrosis







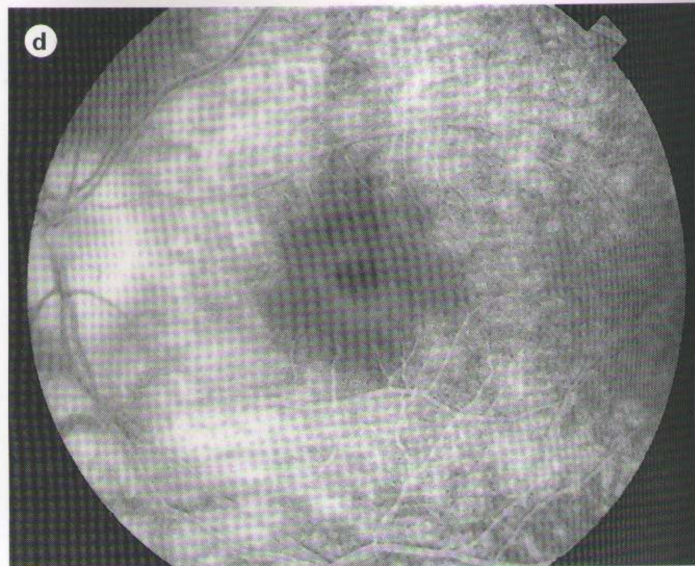


Fig. 10.128
Multiple evanescent white dot syndrome (*see text*) (Courtesy of S. Milewski)

Differential diagnosis

1. **Sarcoidosis**
   - Similarities: multifocal choroiditis and panuveitis.
   - Differences: lesions are usually more numerous in the inferior fundus and CNV does not develop.
2. **Ocular histoplasmosis**
   - Similarities: multifocal punched-out chorioretinal scars and CNV.
   - Differences: absence of intraocular inflammation and fresh lesions do not develop.
3. **Punctate inner choroidopathy**
   - Similarities: multifocal choroidal lesions and CNV.
   - Differences: absence of intraocular inflammation, peripheral involvement and preponderance for young myopic females.

Multiple evanescent white dot syndrome

Multiple evanescent white dot syndrome (MEWDS) is an uncommon, idiopathic, self-limiting, usually unilateral, inflammatory disease. Females are more commonly affected than males, in a 4:1 ratio. Although there is no treatment the prognosis is excellent. It is important to be aware of MEWDS because the subtle signs may be overlooked and misdiagnosis made of a more serious disorder such as retrobulbar neuritis, with its possible implications.

1. **Presentation** is in the third to fifth decades with sudden decreased vision which may be associated with photopsia typically affecting the temporal visual field. In some patients this is preceded by flu-like symptoms.

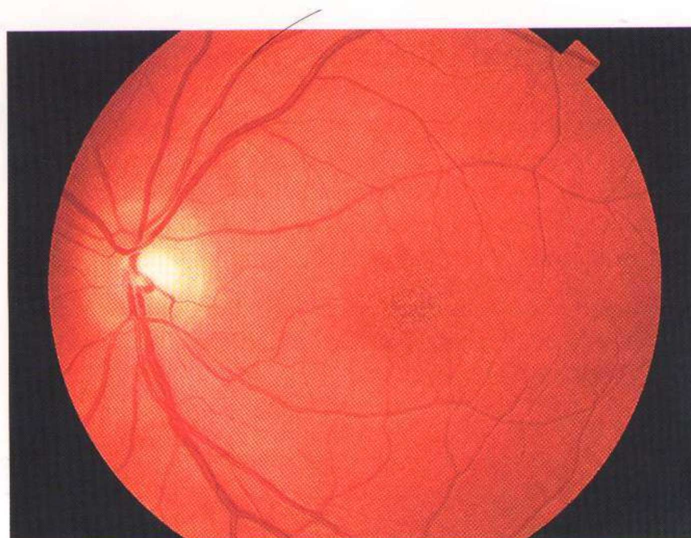
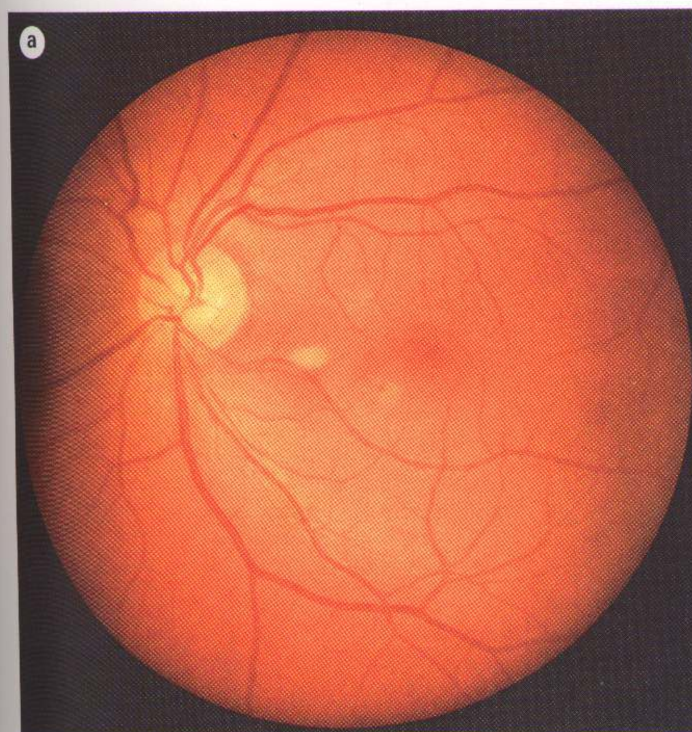


Fig. 10.129
Residual foveal granularity following resolved multiple evanescent white dot syndrome (Courtesy of S. Milewski)

2. **Signs**
   - Numerous, very small, deep, white dots involving the posterior pole but sparing the fovea (Fig. 10.128a). The fovea has a granular appearance which renders the foveal reflex abnormal or absent.
   - Mild vitritis and vasculitis.
   - Optic disc oedema and enlargement of the blind spot.
3. **FA** of active lesions shows a normal early phase (Fig. 10.128b). The late phase shows hyperfluorescence which may have a 'wreath-like' appearance (Fig. 10.128c and d).
4. **ERG** shows a decrease in a-wave amplitude.
5. **Course**. After a few weeks visual acuity recovers, the white dots fade and the disc oedema resolves. The fovea, however, retains its abnormal appearance (Fig. 10.129).



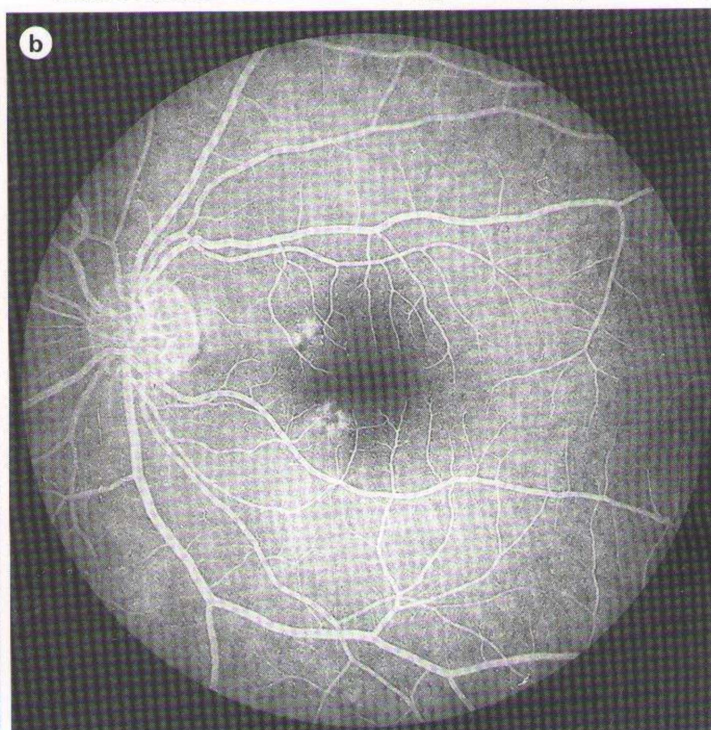


Fig. 10.130
Acute retinal pigment epitheliitis (*see text*) (Courtesy of M. Prost)

Acute retinal pigment epitheliitis

Acute retinal pigment epitheliitis is a rare, idiopathic, self-limiting inflammatory condition of the macular RPE. Although there is no treatment the visual prognosis is excellent. The condition is unilateral in 75% of cases and there is absence of intraocular inflammation.

1. **Presentation** is in the third to fifth decades with sudden impairment of central vision which may be associated with metamorphopsia.
2. **Signs**. The fovea shows a blunted reflex, with discrete clusters of a few, subtle, small, brown or grey spots at the level of the RPE which may be surrounded by hypopigmented yellow haloes (Fig. 10.130a).
3. **FA** shows small hyperfluorescent dots with hypofluorescent centres ('honeycomb' appearance) without leakage (Fig. 10.130b).
4. **EOG** is subnormal.
5. **Course**. Within 6–12 weeks the acute fundus lesions resolve and visual acuity returns to normal. Innocuous residual pigment clumping at the fovea may remain.